CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA

Buprofezin

Chemical Code # 3947**, Document Processing Number (DPN)** 52008
SB 950 # NA
August 4, 1995
Revised, 3/22/01, 10/1/15

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, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Developmental toxicity, rat:	No data gap, possible adverse effect
Developmental toxicity, 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 for the above study types through 260978 (Document No. 52008-0102) were examined. This includes all relevant studies indexed by DPR as of 10/1/15.

In the 1-liners below:
indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T151001
Revised by [redacted], 10/1/15

NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as “possible adverse effect”
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

Analysis of buprofezin metabolism in rats was separated into 3 supplemental studies as indicated below. Buprofezin is rapidly absorbed and excreted (>90% in 48 hr). One study showed that 70-74% of the administered radioactive dose was detected in feces and 21-25% in urine at 96 hr. Another study showed that <1% of the dose remained in the body by 7 days. There was no evidence for bioaccumulation following multiple dietary dosing. Isolated metabolites indicate hydroxylation of the phenyl ring, oxidation of sulfur, and cleavage of the thiadiazin ring followed by conjugation are possible metabolic pathways. Collectively, these three studies provide adequate data to satisfy current requirements for an acceptable animal metabolism study.

Metabolism, Rat

52008-011; 126893a; 851; "Buprofezin: Absorption, Distribution, Metabolism and Elimination in the Rat; part 1, The Fate of ^{14} C-Buprofezin in Animal (Rat) (includes addendum)" by T. Sugimoto et al; Institute of Life Science Research, Nihon Nohyaku Co., Ltd., Osaka, Japan; study ID #NNI-BUPROF-EUP-26; 11/10/92 (original report: 5/82); [^{14}C-phenyl]-buprofezin (2 or 22.5 mCi/mmol; >97% radiochemical purity) suspended in 1 ml of olive oil was administered by gavage to fasted animals at 10 & 100 mg/kg (number of animals varied with the experiment); over 90% of administered dose was excreted by 48 hr at both concentrations; by 96 hr at both concentrations, 70-74% of dose excreted in feces (though a delay at the high dose relative to the low dose was noted through 24 hr), 21-25% in urine, very low amounts excreted as expired ^{14}C-CO $_2$; at 10 mg/kg, 12% of the parent compound was excreted into the feces; C_{max} in blood occurred @ 9 hr for both doses after which concentrations declined biphasically ($t_{0.5}$ =13 & 60 hr); peak levels of radiolabel occurred in tissues @ 5-9 hr post dose, after which tissue levels decreased biphasically with a $t_{0.5}$ of 3.5-15 hr & 15-72 hr for the 2 phases; by 96 hr tissue residue levels were low; metabolite studies revealed hydroxylation of the phenyl ring, oxidation of sulfur, and cleavage of the thiadiazin ring, with evidence of glucuronic and sulfuric conjugation; **Supplemental.** ([redacted], 6/12/95)

52008-011; 126893b; 851; "Buprofezin: Absorption, Distribution, Metabolism and Elimination in the Rat; part 2, The Metabolism of [^{14}]C-Buprofezin in the Rat" by C. Caley & B.D. Cameron; Inveresk Research International, Musselburgh, Scotland; project #136463 (NNI-BUPROF-EUP-26); 11/10/92 (original report: 10/25/88); ^{14}C-buprofezin (lot #CP-845; radiochemical purity >97%) administered by gavage to 5/sex/dose at 10 & 100 mg/kg; in males, 90-91% of dose eliminated by 48 hr (20-21% in urine, 69-71% in feces); in females, 87-89% of dose eliminated by 48 hr (13-14% in urine, 73-76% in feces); elimination faster in males during 1st 24 hr, but equalized by 48 hr; <1% of dose remained in body by 7 days; ÿ30% of male dose and ÿ38% of female dose recovered in bile at 24 hr; chromatography of urine, bile, & feces

indicated extensive conjugation; bile cannulation of 3M/3F revealed that fecal metabolites were likely of bile origin; **Supplemental.** ([redacted], 6/12/95)

52008-011; 126893c; 851; Buprofezin: "Absorption, Distribution, Metabolism and Elimination in the Rat; part 3, Accumulation of Buprofezin in Rats" by T. Sugaya; Institute of Life Science Research, Nihon Nohyaku Co., Ltd., Osaka, Japan; study ID #NNI-BUPROF-EUP-26; 6/90; male rats fed diet containing buprofezin at 200 or 1000 ppm for up to 24 weeks; 3/dose were sacrificed on days 2 and 4 and on weeks 1, 2, 4, 8, 12, 16, & 24; buprofezin levels measured by gas-liquid chromatography after extraction from blood, brain, liver, kidney, adipose tissue, & muscle; detection limit: 0.1 ppm; 200 ppm: only adipose tissue attained levels high enough to consistently detect, remaining stable between 4 days & 24 weeks at a mean concentration of .43-1.10 ppm; an occasional animal showed detectable levels in liver, while kidney, muscle, & brain never showed detectable levels; 1000 ppm: adipose tissue peaked at 10.53 ppm on day 4, declining to 3.40 ppm at 24 weeks; liver retained a stable concentration of 0.21-0.96 over the entire period; kidneys were near or below the detection limit for 8 weeks and undetectable thereafter; brain was near or below the detection limit for 1 week and undetectable thereafter; muscle was near or below the detection limit for 2 weeks and undetectable thereafter (no measurement at 4 weeks); test article thus did not accumulate in any tissue at either concentration; **Supplemental.** ([redacted], 6/14/95)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

52008-002; 126861/143605; 811; "Acute Oral Toxicity Study on Buprofezin in Rats" by K. Tsuchiya; Institute of Life Science Research, Osaka, Japan; study ID #NNI-BUPROF-EUP-10; 11/10/92 (original report: 4/23/82); Buprofezin Technical (99% purity); 10/sex/dose were exposed by gavage to the following doses: 1021, 1429, 2000, 2800, 3920, & 5488 (males only) mg/kg bw; test article was administered as a suspension in olive oil (2 ml/100 g bw); animals were not fasted; body weight changes during the 2-wk observation period not recorded; deaths, male: 1/10, 5/10, 7/10, 9/10, 9/10, & 8/10; deaths, female: 0/10, 1/10, 4/10, 10/10, & 10/10; all deaths had occurred by day 5 post dose; clinical signs, doses over 2800 mg/kg: decreased locomotion, lying on sides, bloody saliva, dacryohemorrhea, hematuria, & diarrhea; doses under 2000 mg/kg: decreased locomotion, salivation, lacrimation, urine incontinence, & diarrhea; **possible adverse effects:** necropsies on decedents revealed duodenal ulcers (some of which were perforated and appeared to retain dosing suspension which in some cases leaked from the perforated area into the abdominal cavity), hemorrhage of the stomach and small & large intestines; necropsies on survivors revealed no abnormalities; reported LD_{50}, M = 1635 (1003-2171) mg/kg, F = 2015 (1769-2299) mg/kg; Toxicity Category not determined; **Unacceptable** (animals were not fasted prior to dosing). ([redacted], 3/15/95, 1/22/96 [clarification of non-fasting status in #143605 changes study from upgradeable to not upgradeable])

52008-025 159289 811 “Buprofezin Technical: Acute Oral Toxicity Study in Rats” by M. Komatsu, Nihon Nohyaku Research Center, Osaka, Japan (study #GA-01, 96-0061; 12/96). Expt. 1: 5 fasted rats/sex/dose were gavaged w/test article (lot #017015; 99.4-99.6% buprofezin) suspended in corn oil at 1000, 1400, 1960, 2744 or 3842 mg/kg. Dose volume was 10 ml/kg. Expt. 2: 5 fasted rats/sex/dose were gavaged w/test article at 2959, 3846, 5000, 6500 or 8450 mg/kg. Dose volume was 20 ml/kg. Dosing was based on the results of Expt. 1. For both experiments, mortality & clinical signs were checked at 1, 3 & 6 hr post dose, and once daily for the following 14 days. Body weights were determined on days 3, 7 & 14, or at death. All animals were subjected to necropsy at termination or death. Microscopic exams of stomach duodenum, jejunum & ileum were conducted on some dead and surviving animals in Expt. 2. Expt. 1: 1 HD male was dead on day 3 (there were no other deaths). The following clinical signs were noted (w/o clear dose dependence): decreased locomotion, tremors, unkempt fur, lacrimation, orbital or nasal discharge, lid closure, soiled anogenital fur, loose stool. All

signs cleared by 9 days. All animals showed weight gains at each time point (the Report considers these gains to have been poor, however). Necropsy of the decedent showed digestive tract fusion as the only possibly test article-related abnormality. Necropsy of survivors did not reveal abnormalities. Expt. 2: Mortality, males: 2/5, 3/5, 3/5, 2/5, 2/5; females: 4/5, 1/5, 5/5, 4/5, 5/5. All deaths had occurred by day 5. Clinical signs (w/o clear dose dependence): decreased or lost locomotion, tremors, abnormal gait, crouching, prone or lateral position, exhaustion, emaciation, dwarfism, salivation, eyeball discoloration, unkempt fur, lacrimation, orbital or nasal discharge, soiled fur, diarrhea or loose stool, incontinence, piloerection, hypothermia, lid closure, hypopnea, dehydration. With the exception of soiled fur, which was present throughout the observation period, clinical signs had cleared by 7 days. Mean weight losses occurred during the observation period at 3846 & 8450 mg/kg, though all groups sustained net gains over the 14 days. Necropsies both of decedents and survivors revealed duodenal adhesions & ulcerations and stomach ulcerations, with jejunal & ileal hemorrhage among decedents. These were confirmed microscopically. Reported LD_{50}, Expt. 2, (M) = 3846 (666-66590) mg/kg; (F) = 2278 (686-7567) mg/kg. These are not considered meaningful due to the lack of dose responsiveness as evidenced by the large 95% confidence limit range. Reviewer-calculated LD_{50} for combined Expt. 1/Expt. 2, (M) = 6476 (3329-12597) mg/kg, (F) = 2894 (1772-4768) mg/kg. Toxicity Category III. **Acceptable.** ([redacted], 2/7/98)

Acute dermal toxicity

52008-002/018; 126863/143610; 812; "NNI-750: Acute Toxicity Study in Rats" by K. Ebino & Y. Shirasu; The Institute of Environmental Toxicology, Ibaraki, Japan; study ID #NNI-BUPROF-EUP-11; 10/29/81; Buprofezin Technical (>99.5% purity) suspended in olive oil (50% w/w); 2-wk observation period; oral administration: 10/sex/dose were gavaged w/1412, 1765, 2206, 2759 or 3447 mg/kg bw (feeding status not addressed); deaths, male: 0/10, 1/10, 6/10, 8/10, 10/10; deaths, female: 0/10, 1/10, 3/10, 8/10, 10/10; clinical observations: decreased locomotion, lacrimation, loose stool, decreased body wt. after 1 wk; **possible adverse effects:** necropsies revealed duodenal ulceration (decedents) & liver-duodenum adhesions (survivors); subcutaneous administration: 10/sex/dose received subcutaneous injections (dorsocervical region) at 2500, 5000, or 10,000 mg/kg bw; no deaths; no clinical signs; all animals gained wt. during both post dose wks; necropsies were negative except for test suspension retention; intraperitoneal administration: 10/sex/dose at 2500, 5000, or 10,000 mg/kg bw; no deaths; no clinical signs; decreased body wt. after 1 wk; necropsies showed swelling of liver & spleen & lung petechiae; percutaneous administration: 10/sex/dose received 1000, 2000, or 5000 mg/kg bw for 24 hr under moistened filter paper; no deaths; no clinical signs; decreased body wt. after 1 wk; necropsies were negative; acute dermal LD_{50}, M/F > 5000 mg/kg bw; Tox. Cat. IV; **Acceptable** (upgraded from unacceptable [3/16/95] w/submission of percutaneous exposure time & conditions)**.** ([redacted] 1/22/96)

Acute inhalation toxicity, rat

52008-002/018; 126864/143606; 813; "Acute Inhalation Toxicity of Buprofezin in Rats" by K. Tsuda; Institute of Environmental Toxicology, Ibaraki, Japan; study ID #NNI-BUPROF-EUP-12; 11/10/92 (original report: 12/20/84); test material contained 90% buprofezin & 10% white carbon (vehicle); 10/sex/dose were exposed to aerosolized test material in a whole body chamber; 4-hr exposure; mean analytical exposure concentrations: 3.57 & 4.57 mg/L; MMAD (GSD): 6.5 um (2.1) & 7.5 um (2.2); 2-wk observation period; no male deaths, 1 high dose female found dead on day 2 post exposure; clinical sign: red staining around nose, clearing w/i 3 days of exposure; all survivors gained weight during both weeks post exposure; necropsy on the decedent not performed because of cannibalism; necropsies on survivors revealed 1 low dose male & 1 high dose female with scattered dark-red patches in the lung; LC_{50}, M/F > 4.57 mg/L; Toxicity Category III; **Acceptable** (upgraded from unacceptable [3/17/95] w/submission of raw data used to calculate analytical chamber concentration). ([redacted], 1/22/96)

Primary eye irritation, rabbit

52008-019; 143611; 814; "Eye Irritation Study in Rabbits [Buprofezin (Technical Grade)]" by D.L. Blaszcak, Bio/dynamics Inc., East Millstone, NJ; project #6570-86; 12/17/86; 0.1 ml instilled into the right lower conjunctival sac of each of 6 males; eyes were washed at 24 hr to remove residual test material; eye irritation exams performed at .1, 24, 48 & 72 hr post dose; fluorescein was used at 24 & 48 hr to aid corneal observations; corneal opacity: grade "+" in 3/6 animals at 1 hr post dose, clearing by 24 hr (confirmed by negative fluorescein readings); iritis: grade 1 in 2/6 and grade "+" in 4/6 at 1 hr, clearing by 24 hr; conjunctival irritation (max. scores: 1/redness, 2/chemosis, 1/discharge, 0/necrosis-ulceration): grade 2 in 1/6 and grade 1 in 5/6 at 1 hr, clearing by 24 hr; Toxicity Category IV; **Acceptable** [redacted], 1/18/96)

Primary dermal irritation

52008-020; 143612; 815; "Primary Dermal Irritation Study in Rabbits [Buprofezin (Technical Grade)]" by D.L. Blaszcak, Bio/dynamics Inc., East Millstone, NJ; project #6569-86; 12/17/86; 0.5 g of test material moistened w/ 0.5 ml saline was applied to a clipped intact dorsal test site (covered w/gauze) on each of 6 males; 4-hr exposure; dermal irritation exams were conducted ~30 min and 24, 48 & 72 hr post patch removal; dermal irritation scores, erythema: grade 1 in 1/6 animals at 0.5 hr post dose, clearing by 24 hr; edema was not observed at any time through 72 hr; Toxicity Category IV; **Acceptable** ([redacted], 1/19/96)

Dermal sensitization

52008-039; 178037; “Skin Sensitization Study with Buprofezin (Technical Grade)”; (D. Blaszcak, *et. al.*; Bio/dynamics Inc., East Millstone, NJ; Project No. 6571-86; 1/12/87); Ten female Hartley albino guinea pigs were tested in the Guinea Pig Maximization Test for allergic contact sensitization to Buprofezin Technical (lot no. 194-2, purity: 99.3%). Induction was undertaken by intradermally injecting 0.1 ml of 5% (w/v) of the test material in propylene glycol at four sites on each animal on day 0. The potential for a response was enhanced by intradermally injecting 0.1 ml of Freund’s complete adjuvant:water (1:1) at two sites. On day 7, induction was furthered by topically applying the saline-moistened test material and maintaining the test material under an occlusive wrap for 48 hours. In order to enhance the potential for induction, the topical site was irritated by the application of 10% (w/v) sodium lauryl sulfate in petrolatum on day 6. On day 21, the animals were challenged by topical exposure of the saline-moistened test material for 24 hours under an occlusive wrap. Concurrent controls were treated in the same manner in order to ascertain the irritation potential of the treatment. Likewise, 10 additional female guinea pigs were treated with the positive control, dinitrochlorobenzene (DNCB), according to the same induction and challenge schedule as the test material. Due to an equivocal response to the test material, the animals were re-challenged on day 28. In the challenge, 5 of the 10 animals exhibited very slight erythema during the 48 hour observation period. In the re-challenge, 3 of the 10 animals exhibited the same degree of irritation. A positive response was elicited by DNCB. **The results do not indicate an allergic sensitization response to the test material. Study acceptable.** [redacted], 3/7/01)

Supplemental Acute Toxicity Study

52008-002; 126863; "Acute Toxicity Study in Mice" by K. Ebino & Y. Shirasu; The Institute of Environmental Toxicology, Ibaraki, Japan; study ID #NNI-BUPROF-EUP-11; 10/29/81; test compound suspended in olive oil (50% w/w); doses: 2500, 5000, & 10,000 mg/kg bw administered to 10/sex/dose for all exposure routes; 2-wk observation period; oral administration (gastric intubation): no deaths; clinical signs: decreased locomotion, loose stool; some animals showed body wt. decrements after 1 week (though none showed decrements after 2 wks.); terminal necropsies revealed 1 high dose male w/duodenal ulceration; subcutaneous administration (dorsocervical injection): no deaths; no clinical signs; some animals showed body wt. decrements after 1 week (though none showed decrements after 2 wks.); terminal necropsies were negative; intraperitoneal administration: no deaths; no clinical signs;

some animals showed body wt. decrements after 1 week (though none showed decrements after 2 wks.); terminal necropsies revealed liver swelling in all animals at the high dose and in 5/10 males at the mid dose; reported LD_{50}'s for all exposure routes, M/F > 10,000 mg/kg bw; Toxicity Categories not assigned; **Supplemental.** ([redacted], 3/16/95)

SUBCHRONIC STUDIES

Rat subchronic dietary toxicity study

52008-003; 126865; 821; "A 90-Day Oral Toxicity Study of Buprofezin Rats" by M. Watanabe; Preclinical Research Laboratories, Central Institute for Experimental Animals, Kawasaki, Japan; study ID#NNI-BUPROF-EUP-13; 11/10/92 (original report: 7/18/86); Buprofezin Technical (lot #28, 99% purity) administered in diet to 10/sex/dose at 0, 40, 200, 1000, & 5000 ppm; 90-day exposure period; no deaths; no clinical signs; body weights were slightly reduced at 1000 & 5000 ppm; food intake was slightly reduced at 200, 1000, & 5000 ppm; high dose livers & thyroids were enlarged (also male thyroids at 1000 ppm); several organ weights (including liver & thyroid) & organ-body weight ratios were elevated, occasionally at 1000 ppm; livers displayed hepatocellular enlargement & thyroids displayed increased follicular epithelial cell height and hyperplasia, both at 1000 & 5000 ppm; round epithelial cells were elevated in male urine at 1000 & 5000 ppm; serum chemistry showed several changes including elevation of cholesterol & phospholipids (statistically significant at 5000 ppm) & lowering of plasma glucose (statistically significant in males at 200, 1000, & 5000 ppm) and triglycerides (statistically significant at 5000 ppm); hemoglobin, hematocrit, & erythrocyte counts were slightly lowered at 5000 ppm; NOAEL, M/F > 5000 ppm; NOEL, M/F = 40 ppm (3.4 mg/kg for males, 4.1 mg/kg for females; lowered plasma glucose and food consumption); **Acceptable.** ([redacted], 3/22/95)

Dog subchronic oral toxicity study

52008-004; 126871; 821; "Toxicity Study by Oral Administration to Beagle Dogs for 13 Weeks" by A. Broadmeadow; Life Science Research, Eye, Suffolk, England; study ID #NNI-BUPROF-EUP-14; 11/10/92 (original report: 4/17/85); Buprofezin technical (lot #28, 99% purity); administered in gelatin capsules to 4/sex/dose at 0 (vehicle control), 2, 10, 50, or 300 mg/kg/day for 13 wks; no deaths; clinical signs: subdued mood at 50 mg/kg (2/4 males & females) and high dose (HD; 3/4 males, 4/4 females), ataxia at 50 mg/kg (1/4 males) and HD (4/4 males, 3/4 females) (**possible adverse effect**), and distended abdomen at 50 mg/kg (1/4 males) and HD (3/4 males, 2/4 females); food & water consumption were slightly lowered @ HD; HD body weight gain in both sexes was suppressed; slightly prolonged prothrombin times in HD females; mean alkaline phosphatase (AP) was elevated in both sexes @ HD and in males @ 50 mg/kg; normative AP decline w/maturity was suppressed in males @ 10 mg/kg & in females @ 2 mg/kg; alanine aminotransferase was elevated @ HD; absolute & relative liver wts. were elevated in both sexes at the 2 top doses; kidney showed evidence of increased wt. @ HD and thyroid at the top 2 doses; HD uterus wts. were suppressed; ophthalmoscopy, urinalysis, & necropsies were negative; histopath. revealed homogeneity of hepatocytic cytoplasm @ 50 & 300 mg/kg (3/4 & 4/4, both sexes), intracytoplasmic eosinophilic bodies @ 50 (1 female) & 300 mg/kg (all dogs); NOAEL, M = 10 mg/kg/day (ataxia & subdued mood), F = 50 mg/kg/day (ataxia & subdued mood); NOEL, M/F = 10 mg/kg/day (elevated liver & thyroid wts. & AP activity); **Acceptable.** ([redacted], 5/5/95)

Rat 21-day repeated dosing dermal toxicity study

52008-039; 178038; “T75 Buprofezin: Toxicity Study by Dermal Application to CD Rats for 24 Days Followed by a 2-Week Reversibility Period.”; (C.R. Willoughby; Pharmaco LSR, Toxicology Services Worldwide, Eye, Suffolk, IP 23 7 PX, England; Report No. 94/NHH076/1040; 6/29/95); The skin of 5 CD rats/sex/group was treated for 6 hours/day for 24 days with 0, 100, 300 or 1000 mg/kg/day of Buprofezin Technical (batch no. 2AD0004P, purity:

99.0%) under an occlusive wrap. The test material was suspended in a 2% gum arabic aqueous solution. In addition, 5 animals/sex were included in the control and high dose groups and held for 2 more weeks after the termination of the dosing. No deaths occurred in the study. No treatment-related effects on clinical signs, mean body weight, food consumption, hematology, clinical chemistry, or urinalysis were noted. In the necropsy, the mean relative kidney weight was increased for the 1000 mg/kg females ($p<0.05$). In the histology examination, there was an increased incidence of focal hepatocellular necrosis for the 1000 mg/kg females (0: 1/5, 1000: 3/5). The animals in the reversibility phase were observed, their body weight and food consumption were measured and organ weights were recorded. No treatment-related effects were noted. **No adverse effect indicated. NOEL: Systemic** (M) 1000 mg/kg/day (based upon no treatment-related effects at highest dose tested); (F) 300 mg/kg/day (based upon increased incidence of focal hepatocellular necrosis in the 1000 mg/kg females); **Dermal** (M/F) 1000 mg/kg (based upon no treatment-related effects at the highest dose tested); **Study acceptable.** ([redacted], 3/1/01)

CHRONIC STUDIES

Chronic, rat

52008-006; 126875; 835; "24 Months Oral Chronic Toxicity and Oncogenicity Dietary Study on ST-29285 (Buprofezin) in Rats" by M. Watanabe, Preclinical Research Labs, Central Institute for Experimental Animals, Kawasaki, Japan; NNI-BUPROF-EUP-16; 11/10/92 (original: 4/30/82); ST-29285 (Buprofezin Technical; >99% purity); 0, 5, 20, 200, or 2000 ppm administered in feed to 55/sex/dose; interim sacrifices: 6 months (5/sex/dose) and 12 months (10/sex/dose); terminal sacrifice of remainder at 24 months; mortality increased slightly w/dose in females (21/40, 22/40, 22/40, 26/41, & 27/40); body weight was statistically suppressed in high dose (HD) males thru wk 5 and in HD females thru 6 months and occasionally over the following 18 months; clinical signs were not detected; statistically significant increases in HD thyroid weight at 6, 12, & 24 months (also in 200 ppm females at 12 months), and in liver weight at 12 & 24 months; hypertrophy of centrilobular hepatocytes seen at all sacrifices; hyperplasia of HD thyroid follicular epithelium seen at all sacrifices; also, hepatocyte necrosis & hyperplastic nodules in both sexes, interstitial pneumonia in males, interstitial heart edema and other heart effects in females were all noted at the high dose; no sign of renal or hepatic dysfunction detected by PSP or BSP excretion; tumor incidence was not affected by treatment; NOAEL, M/F > 2000 ppm; NOEL, M/F = 20 ppm (based on histopathologic signs in various organ systems); **Acceptable. ([redacted], 4/28/95)

Chronic, dog

**52008-005; 126872; 831; "IET 7907 (Buprofezin): Toxicity in Oral Administration to Beagle Dogs for 107 Weeks" by H.A. Cummins; Life Science Research, Stock, Essex, England; study ID #NNI-BUPROF-EUP-17; 11/10/92 (original report: 3/25/82); IET 7907 (lot #1 & 4; >99% purity) administered in gelatin capsules to 6/sex/dose at 0 (vehicle control), 2, 20, or 200 mg/kg/day for 107 wks; no deaths; no clinical signs; HD (high dose) males gained less weight than controls during the 1st 6 months & HD females gained less during the 2nd year; HD males consumed slightly less food; water consumption was unaffected; hematology, urinalysis, ophthalmoscopy, and macroscopic pathology were negative; alkaline phosphatase was elevated in both sexes at the top 2 doses throughout the treatment period and alanine aminotransferase at the HD from wk. 52 onward; thyroxine was lowered at the HD in females from wk. 52 onward; bromosulphonphthalein retention was elevated (not statistically significant) in females after 103 wks at the top 2 doses & in males at the HD; in females absolute liver weights were elevated at the top 2 doses and relative liver weights at all doses; relative thyroid weights were elevated at the HD in both sexes; bile duct hyperplasia occurred in both sexes at the top 2 doses; centriacinar hepatocyte enlargement occurred in males at the top 2 doses and at the HD in females; NOAEL, M/F > 200 mg/kg/day; NOEL, M/F = 2 mg/kg/day (elevated

serum alkaline phosphatase & liver wt. and liver structural changes); no adverse effects; **Acceptable.** ([redacted], 5/11/95)

Oncogenicity, rat

See Chronic, rat above.

Oncogenicity, mouse

52008-007; 126878; 832; "NNI-750 (Buprofezin): 24 Months Oral Chronic Toxicity and Oncogenicity Dietary Study in Mice" by A. Yoshida; The Institute of Environmental Toxicology, Tokyo, Japan; study ID #NNI-BUPROF-EUP-15; 11/10/92 (original report: 4/26/90); NNI-750 (lot #5 & 7; 99.5% purity) administered in diet at 0, 20, 200, 2000, & 5000 ppm; 80/sex/dose; 24 months (104 wks.); at 52 & 104 wks. 10/sex were subjected to urinalysis, hematology, blood chemistry, & necropsy; death rate was not affected by treatment; 5000 ppm: retarded growth, decreased urine specific gravity, elevated liver weight and hepatocellular swelling & hyperplasia, and slight anemia in females (the latter after 52 wks only); 2000 ppm: slightly retarded growth and elevated liver weight and hepatocellular swelling & hyperplasia; 200 ppm: elevated liver weight in males after 52 wks.; **possible adverse effect: liver adenomas were elevated in females at the top 2 doses (2/80, 2/80, 1/80, 7/80, & 8/80; $p<0.05$); treatment-induced oncogenesis not observed in other tissues; oncogenic NOAEL = 200 ppm (liver adenomas in females); non-oncogenic NOAEL = 200 ppm (hepatotoxicity in both sexes); NOEL, M = 20 ppm & F = 200 ppm (liver weight increase at 52 weeks); **Acceptable.** ([redacted], 5/19/95)

GENOTOXICITY

Gene mutation

52008-010; 126884; 842; "Buprofezin: An Evaluation in the Salmonella Mutagenicity Assay" by R.D. Callander; ICI Central Toxicology Laboratory, Cheshire, UK; study ID #NNI-BUPROF-EUP-21; 11/10/92 (original: 7/27/88); Buprofezin Technical (lot #223-1; 99.8% purity); after preliminary cytotoxicity tests at 1.6-5000 mg buprofezin/plate in the TA100 strain were negative, 5 Salmonella typhimurium tester strains (TA98, 100, 1535, 1537, & 1538) were exposed -/+ S9 microsomes to 1.6, 8.0, 40, 200, 1000, & 5000 (precipitate present) mg/plate for 64-68 hr @ 37:C in 2 separate experiments; all doses and positive controls were run in triplicate; there were no positive increases in the # of histidine revertants in any tester strain -/+ S9; successful positive controls were run for each tester strain; buprofezin is not mutagenic in the Ames assay under the present conditions; no adverse effects; **Acceptable. ([redacted], 6/14/95)

52008-010; 126885; 842; "Buprofezin: Assessment of Mutagenic Potential Using the L5178Y Mouse Lymphoma Cell Assay" by M.F. Cross; ICI Central Toxicology Laboratory, Cheshire, UK; study ID #NNI-BUPROF-EUP-22; 11/10/92 (original: 7/29/88); Buprofezin Technical (lot #223-1; 99.8% purity); preliminary cytotoxicity determinations: 2 separate expts. were conducted; -S9, clear cytotoxicity evident at 31.6 mg/ml and above, though possibly present as low as 13.3 mg/ml in 1 expt.; +S9, clear cytotoxicity at 100 mg/ml (solubility limit), possibly present as low as 23.7 mg/ml; mutation determinations: duplicate suspension cultures were exposed to buprofezin -S9 (2 expts., range: 13.3-42.2 mg/ml) and +S9 (2 expts., range: 17.8-100 mg/ml) for 2 hr, after which the cells were washed, allowed an expression time of 72 hr, and exposed at a density of 104 cells/ml to selective medium containing 2 mg/ml trifluorothymidine and apportioned to 96-well plates; even at concentrations that were markedly cytotoxic, no increase in mutation frequency (as would be reflected in a decrease in growth-negative wells) was detected, despite the success of the positive controls; no adverse effects; **Acceptable. ([redacted] 6/15/95)

Chromosome damage

**52008-010; 126888; 843; "Buprofezin: An Evaluation in the In vitro Cytogenetic Assay in Human Lymphocytes" by C.A. Howard & C.R. Richardson; ICI Central Toxicology Laboratory,

Cheshire, UK; study ID #NNI-BUPROF-EUP-23; 11/10/92 (original: 7/29/88); Buprofezin Technical (Lot #223-1, 99.8% purity); blood was withdrawn on the day of experimentation from 1 male & 1 female donor and lymphocyte cultures initiated with hemagglutinin; 44 hr after culture initiation buprofezin was added to duplicate cultures at 0, 0.1, 0.5, 1, 5, 10, 20, 40, 60, 80, & 100 (solubility limit) mg/ml, -/+ S9 microsomes, though only 0, 10, 60, & 100 mg/ml were subjected to karyotyping; exposure time: between 3 hr, 5 min and 3 hr, 20 min; .2 hr prior to harvesting @ 72 hr, cells were arrested in metaphase w/10 mg/ml colchicine and chromosome spreads prepared; 100 metaphases/culture were examined microscopically; no buprofezin-related significant increase in mean % abnormal cells or in aberrations/cell (excluding gaps); positive controls (-S9, 0.5 mg/ml mitomycin C; +S9, 100 mg/ml cyclophosphamide) were functional; buprofezin is not considered clastogenic under the present conditions; no adverse effects; **Acceptable.** ([redacted], 6/19/95)

52008-010; 126887; 843; "Buprofezin: Micronucleus Test" by Y.F.X. Saski; The Institute of Environmental Toxicology, Tokyo, Japan; study ID #NNI-BUPROF-EUP-25; 11/10/92 (original: 11/8/83); Buprofezin Technical (lot #17; 99.5% purity); Expt. #1: 6/sex/dose were exposed to a single treatment w/buprofezin at 0 (vehicle control, 2% Tween 80, dosed at 20 ml/kg), 6400, 8000, or 10,000 mg/kg (the high dose was run separately and included its own vehicle controls); bone marrow smears prepared 12, 24, 48, or 72 hr after the high dose treatments or 24 hr after treatment at the other doses; statistically significant increases in % micronucleated polychromatic erythrocytes noted in males at 6400 & 8000 mg/kg (0.03% in controls vs. 0.15 & 0.20) and in both sexes at 10,000 mg/kg (males, 0.12 vs. 0.27; females, 0.10 vs. 0.30); a repeat expt. (same doses, 24-hr harvest) showed no effect (no positive controls run); Expt. #2: 8/sex/dose were dosed w/buprofezin on 4 consecutive days at 0 or 10,000 mg/kg/day (no positive controls); bone marrow smears prepared 12, 24, 48, or 72 hr after the final treatment; no statistically significant change in micronuclei, though no positive controls were run; no adverse effects indicated; **Unacceptable and not upgradeable** (positive controls were not run in some tests). ([redacted], 6/16/95)

DNA damage or miscellaneous effects

******52008-010; 126890; 843; "Buprofezin: Assessment for the Induction of Unscheduled DNA Synthesis [UDS] in Primary Rat Hepatocyte Culture" by R.W. Trueman; ICI Central Toxicology Laboratory, Cheshire, UK; study ID #NNI-BUPROF-EUP-24; 11/10/92 (original: 11/15/88); Buprofezin Technical (lot #223-1; 99.8% purity); fresh hepatocytes attached to coverslips were exposed to buprofezin and 3H-thymidine for 17-20 hr, washed, fixed, dried, and processed for autoradiography; the high dose (10^{-5} M) was based on observation of clear cytotoxicity at 10^{-4} and 10 3 M and a modicum of toxicity at 10 5 M; final doses: 0 (vehicle control, 0.5% DMSO), 10^{-8}, 10^{-7}, 10^{-6}, & 10^{-5} M; UDS analyzed in .100 cells/treatment (25-50 cells/coverslipped slide, 2-3 slides/treatment); 3 independent studies over this dose range showed that the mean net nuclear grain count (nuclear count - cytoplasmic count) was less than 0, indicating unequivocal absence of UDS; positive control, 10 6 M 6-p-dimethylaminophenylazobenzthiazole, was functional; buprofezin does not induce UDS under the conditions tested; no adverse effects; **Acceptable.** ([redacted], 6/20/95)

REPRODUCTIVE TOXICITY, RAT

******52008-026 159290 834 “Two-Generation Reproduction Study in Rats with Buprofezin” by S. Toyohara, Toxicology Research Center, Imamichi Institute for Animal Reproduction, Ibaraki, Japan (study #T-1108, report #458; 9/8/97). Test article (lot #2AD0004P; 99.0% buprofezin) was administered in the diet to 26 rats/sex/dose at 0, 10, 100 or 1000 ppm. Dosing was commenced 10 wks before mating of the P generation and continued through weaning of the F2 generation. Thus the feeding period for the both generations was 19 weeks (10 wks premating, 3 wks mating, 6 wks gestation + nursing). Litters were culled on day 4 to 4/sex. Standard observations for clinical and reproductive effects were made. There were neither exposure-caused deaths nor clinical signs among P or F1 parentals or their offspring.

Occasional statistically significant increased body weights & food consumption among dosed groups compared to controls were noted, though a test article etiology was unclear. Mean compound intake was proportional to dose level: P males: 0.64, 6.46, 66.00 mg/kg/day; P females: 0.92, 9.21; 93.11 mg/kg/day; F1 males: 0.75, 7.42, 73.97 mg/kg/day; F1 females: 1.02, 10.20 & 99.57 mg/kg/day. P & F1 parental estrus cycles and F1 newborn preputial separation & vaginal opening were unaffected. Mating & fertility indices were at or near 100% for all dose groups. Neither sperm production nor function was affected by exposure. No significant differences among dose groups were noted for gestation length, # live newborns, # dead pups, # implants, pup viability on days 0, 4 or 21, or external abnormalities. Pup weights were significantly higher than controls at the MD & HD (F1 males, day 0) and at the HD (F1 females & F2 males, days 0 & 4). F2 pup weight gains were statistically suppressed in both sexes on days 7-14 of lactation. HD/P male liver & kidney weights & female adrenal weights and HD/F1 male kidney wts showed statistically significant changes. No test article-related macro- or micropathologic changes were detected among parents or offspring. Parental NOEL = 100 ppm (organ weight effects). Reproductive/fetal NOEL (M/F) = 100 ppm (F2 pup weights at birth). **Acceptable.** ([redacted], 2/11/98)

52008-009; 126882; 834; "Two-Generation Reproduction and Teratogenicity Studies in Rats with Buprofezin" by T. Takeshima; Institute for Animal Reproduction, Ibaraki-ken & Institute of Environmental Toxicology, Tokyo, Japan; study ID #NNI-BUPROF-EUP-20; 11/10/92 (original report: 4/14/82); NNI-750 (lot #6; 99.1% purity); 0, 10, 100, or 1000 ppm administered in diet to F0 generation for 13 wks. prior to mating and continued in all animals through the F2b generation; 30/sex for each mating; 10 dams bearing F1b or F2b fetuses were necropsied and the fetuses examined on gestation day 21; histopath not performed; no deaths or clinical signs related to exposure were evident during any part of the study; HD body weights were suppressed compared to controls for the F0 (both sexes, early measurements); a possible suppressive effect on weight gain was present during both F0 pregnancies; F2a pup weights were affected at all doses and all HD pups experienced suppressed weight gain during lactation; food intake was suppressed in F0 animals at all doses during the 1st 3 wks.; no effect on male fertility or female pregnancy performance; increased mortality and decreased survival of F1a pups at 10 and 1000 ppm was due to difficult delivery or poor nursing and probably not test article-related; kidney and liver wts. were consistently elevated; no adverse effects; reproductive NOEL > 1000 ppm (no changes in reproductive indices); parental NOEL < 10 ppm (reduced body weights in F1b); developmental NOEL < 10 ppm (reduced fetal weight in F1b & pup weight in F2a); **Unacceptable** (histopathology not performed)**.** ([redacted] 6/2/95)

DEVELOPMENTAL TOXICITY

Rat

52008-008; 126984; 833; "Buprofezin: Teratology Study in the Rat" by T.J. Wightman; Life Science Research, Eye, Suffolk, England; study ID #NNI-BUPROF-EUP-18; 11/10/92 (original report: 5/14/87); Buprofezin Technical (lot #28; 99% purity); 0 (vehicle control, 10 ml/kg 2% aqueous gum arabic mucilage), 50, 200, or 800 mg/kg/day administered by gavage to pregnant animals from day 6-15 of gestation; 22/dose; sacrifices performed on gestation day 20; maternal deaths: 1 high dose (HD) animal; maternal clinical signs (all appearing at the HD): loose feces, urogenital staining, lethargy, hunched posture, thin appearance, piloerection; body weight was static at the HD between initiation of treatment and gestation day 10, after which the rate of weight gain was slightly less than controls; significant reduction in HD food intake during treatment and post-treatment phases and a transient (day 14) reduction in 200 mg/kg animals; significant increase in water consumption during treatment at 200 & 800 mg/kg; **possible adverse effects: 4/21 dams showed total litter resorption at the HD, HD dams carrying young to term showed early post-implantation loss and reduced litter size & fetal weight; HD fetuses showed increases in subcut. edema, small fetuses w/space between bodywall & organs, and incomplete ossification; 200 mg/kg fetuses showed slight reduction of supra-occipital &

intraparietal bone ossification; maternal/developmental NOAEL = 200 mg/kg/day (total litter resorption & other litter effects); maternal NOEL = 50 m/kg/day (increased water consumption); developmental NOEL = 50 mg/kg/day (reduced ossification); **Acceptable.** ([redacted], 5/25/95)

Rabbit

52008-008; 126880; 833; "Buprofezin: Teratology Study in the Rabbit" by F.W. Ross; Life Science Research, Eye, Suffolk, England; study ID #NNI-BUPROF-EUP-19; 11/10/92 (original report: 4/18/86); Buprofezin Technical (lot #28; 99% purity); 0 (vehicle control, 5 ml/kg 2% aqueous gum arabic), 10, 50, or 250 mg/kg/day administered by gavage to pregnant animals from day 6-19 of gestation; 17/dose; deaths: 2 animals receiving 10 mg/kg/day (not test article-related); initial weight loss & overall reduced weight gain occurred at the high dose (HD); HD food intake was suppressed until day 13; abortions: 1 animal at 50 mg/kg/day; **possible adverse effect: total resorptions: 2 animals at the HD; excluding total resorptions, litter responses (# implantations & viable young, extent of pre- and post-implantation loss, and fetal & placental weights) and fetal morphogenesis were unaffected by treatment; maternal/developmental NOAEL = 50 mg/kg/day (total litter resorption); maternal NOEL = developmental NOEL = 50 mg/kg/day (reduced maternal body weight & total litter resorption); **Acceptable**. ([redacted] 5/23/95)

NEUROTOXICITY

Acute neurotoxicity, rat

Buprofezin does not have structural alerts for delayed neurotoxicity, such as organophosphates. There was no evidence of neurotoxicity in the other toxicity studies that have been conducted with buprofezin . It was therefore considered that buprofezin does not have potential to induce neurotoxicity in mammals (European Food Safety Authority, EFSA Journal 8: 1624 (2010)).

90-day neurotoxicity, rat

** 52008-0101; 259771; “Buprofezin Technical: Neurotoxicity Study by Dietary Administration to CD Rats for 13 Weeks”; (W.N. Hooks; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Project ID No. NHH/115; 3/30/05); Ten Crl: CD (SD)IGS BR rats/sex/group received 0, 50, 500, or 5000 ppm of Buprofezin Technical (batch no. 010100; purity: 99.9%) in the diet for 13 weeks (M) 0, 3.49, 35.3, 358 mg/kg/day, (F) 0, 4.38, 42.8, 433 mg/kg/day). The mean body weight gains of both sexes in the 5000 ppm group were less than those of the control group over the course of the study ($p<0.01$). The food consumption of the males in the 5000 ppm group was less than that of the control group ($p<0.05$) as well. Although the body temperature and landing foot splay of either males or females in the 5000 ppm group were significantly different from the control group values at various times during the study, the FOB measurements did not demonstrate any apparent treatment-related effect. The motor activity measurements did not indicate any treatment-relate effect. The mean brain weight and brain morphometric measurements were not affected by the treatment. The histopathological examination did not reveal any treatment-related neurological lesions. **No adverse effect indicated. Rat Subchronic Neurotoxic NOEL:** (M/F) 5000 ppm ((M) 358 mg/kg/day, (F) 433 mg/kg/day) (based upon the lack of any treatment-related neurotoxic effects in either sex of the 5000 ppm treatment group); **Study acceptable**. ([redacted], 10/23/14)

Developmental neurotoxicity, rat

No study submitted nor required at this time.

Delayed neurotoxicity, hen

No study submitted nor required at this time.

IMMUNOTOXICITY

**** 52008-0102; 260978**; "Buprofezin: 4 Week Dietary Immunotoxicity Study in the Sprague Dawley Rat"; (E.L. Moore; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Project ID No. LMS0019; 3/17/11); Ten Crl:CD (SD) rats/sex/group received 0, 200, 1000 or 5000 ppm of Buprofezin Technical (lot no. 910009; purity: 99.5%) in the diet for 4 weeks ((M) 0, 15.8, 78.1, 343 mg/kg/day, (F) 0, 15.4, 79.0, 346 mg/kg/day). Another 8 animals/sex were dosed by intraperitioneal injection with 50 mg/kg of cyclophosphamide in 0.9% saline on day 27 as the positive control group. On day 25, five days before necropsy on day 29, each animal received an iv injection of $2x10^8$ sheep red blood cells (SRBC). SRBC-specific IgM plaques were determined for each animal by incubating a spleen cell suspension preparation with guinea pig complement and SRBC. No deaths occurred during the treatment period. The mean body weight gains of both sexes in the 5000 ppm group were less than those of the control group over the course of the study ($p<0.01$). The food consumption of both sexes in the 5000 ppm group was also less than that of the control group. There were no treatment-related lesions noted in the necropsy examination. In the plaque-forming cell assay, the females demonstrated a dose-related decline in cells/spleen, plaque-forming cells/10^6 spleen cells and plaque-forming cells/spleen (NS, $p<0.05$). **Possible adverse effect:** immunosuppression noted for the females**.** The positive control was functional. **Study acceptable.** ([redacted], 7/22/15)

ENDOCRINE DISRUPTOR STUDIES

No study submitted nor required at this time.

SUPPLEMENTAL STUDIES

No studies submitted.