COMPARATIVE SAFETY OF RECENT PESTICIDES FOR ASIAN CITRUS PSYLLID CONTROL

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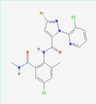
LITTLE VECTOR, BIG PROBLEM

The Asian citrus psyllid causes minor damage to growing shoots of citrus trees, but it acts as a vector for *Candidatus Liberibacter*, which causes citrus greening disease, commonly called huanglongbing. Infected trees always die. Florida scientists detected the vector in 1998, but large-scale losses from huanglongbing were not seen until 2005. Despite quarantine efforts by California officials, the vector is established in some Southern California residential areas, and poses a threat to the California citrus industry. The vector has not established itself in major commercial areas, and to date, the vectored disease has not been reported in California.

THE CONTROL ARSENAL

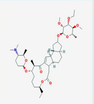
- 13 pesticides recommended by University of California Statewide IPM
- 8 of these pesticides are older (pre-1995): mostly cholinesterase inhibitors or pyrethroids
- The 5 most recent pesticides, detailed here, represent 4 different chemical classes
- Treatment strategies involve:
  - A combination of foliar and systemic approaches
  - Use of a variety of chemical classes to control resistance

THE FIVE MOST RECENT INSECTICIDES ENLISTED



Chlorantranilipole: Activates ryanodine receptors, which respond by releasing stored calcium in insect muscle tissue, causing death by paralysis. This foliar insecticide is applied at 3 to 4.5 oz/acre.

Imidacloprid: This established neonicotinoid insecticide is normally applied as a soil drench for systemic activity. Maximum application rate is 0.5 lb AI/acre/yr.



Spinetoram: A spinosyn insecticide which kills insects by excitation of the nervous system [allosteric regulation of nicotinic Acetylcholine receptor agonists]. Selective since it must be ingested to be effective, so predatory arthropods are largely spared. Maximum application rate is 6 oz/acre as foliar spray.

Spirotetramat: tetronic acid lipid biosynthesis inhibitor. Foliar application for systemic action. Application rate 10 oz/acre.

Thiamethoxam: systemic neonicotinoid insecticide commonly applied as soil drench, at no more than 0.172 lb I/acre/yr.

CHRONIC, REPRODUCTION, AND DEVELOPMENTAL STUDY ENDPOINTS

CHLORANTRANILIPROLE

Species	Study Type, Exposure	Sex	(mg/kg/day) NOEL	(mg/kg/day) LOEL	Findings at LOEL and characteristic findings at higher dose levels
Rat	Chronic/ oncogenicity, 22.5 months	M	7.7	39	LOEL: Microvesiculation of adrenal cortex.
		F	51	212	LOEL: Elevated relative liver weights.
Mouse	Oncogenicity, 18 months	M	26	158	LOEL: Increased liver weights. Other major findings at 158-935 mg/kg/day: hepatocellular hypertrophy, hepatocellular eosinophilic foci.
		F	33	196	LOEL: Increased liver weights.
Dog	Chronic, 12 months	M	317	1164	Increased liver weights, increased serum alkaline phosphatase at LOEL = highest dose tested.
		F	278	1233	
Rat	Reproduction, two generation	M	< 18	N/A	Microvesiculation of adrenal cortex *zona fasciculata* at ≥ 238 mg/kg/day (F0) and ≥ 18 mg/kg/day (lowest dose tested) (F1). Degree did not exceed minimal to mild, even at highest dose of 1199 mg/kg/day. Adrenal weights were elevated at ≥ 238 mg/kg/day.
		F	78	318	LOEL: increased weights of livers and adrenals.
		(F)	1594	N/A	**Reproductive Effects** LOEL ≥1594 mg/kg/day (no effects at any dose level)
		(F)	318	1594	**Pup growth and viability** LOEL = 1594, based on about 8% pup body weight decrement in F1 pups only.
Rat	Developmental Toxicity	F	1000	N/A	NOEL for **maternal** toxicity = highest dose tested.
		-	1000	N/A	NOEL for **developmental** toxicity = highest dose tested.
Rabbit	Developmental Toxicity	F	1000	N/A	NOEL for **maternal** toxicity = highest dose tested.
		-	1000	N/A	NOEL for **developmental** toxicity = highest dose tested.

IMIDACLOPRID

Species	Study Type, Exposure	Sex	(mg/kg/day) NOEL	(mg/kg/day) LOEL	Findings at LOEL and characteristic findings at higher dose levels
Rat	Chronic/ oncogenicity, 24 months	M	5.7	17	LOEL: Mineralized particles in thyroid glands. Other major findings at 103 mg/kg/day: Body weight decrement, cholangiocellular carcinomas in 2 males vs. none in any other groups.
		F	25	73	LOEL: Mineralized particles in thyroid glands. Other major findings at 144 mg/kg/day: Body weight decrement.
Mouse	Oncogenicity, 18 months	M	143	286	LOEL: 29% body weight gain decrement, slight periacinar hepatocyte hypertrophy, increased mortality.
		F	143	286	LOEL: 26% body weight gain decrement, food consumption decrement.
Dog	Chronic, 12 months	M	15	≈55	LOEL: slight increase in liver weights and of liver cytochrome P-450
		F	15	≈55	
Rat	Reproduction, two generation	M	18	50	LOEL: Slight decrement in body weight.
		F	25	68	LOEL: Slight decrement in body weight.
		(F)	68	N/A	**Reproductive Effects** LOEL = highest dose tested (no effect)
		(F)	25	68	**Pup growth and viability** LOEL = 68 based on slight decrements in body weights of pups.
Rat	Developmental Toxicity	F	26	94	LOEL for **maternal** toxicity = 94 mg/kg/day based on reduced body weight gain and reduced food consumption.
		-	26	94	LOEL for **developmental** toxicity = 94 mg/kg/day based on slightly increased incidence of wavy ribs. Ratio of males was noted to be slightly elevated [51% in controls vs. 59% in 94 mg/kg/day group].
Rabbit	Developmental Toxicity	F	20	64	LOEL for **maternal** toxicity = 64 mg/kg/day, based on deaths of 2/16 does, reduced food consumption, body weight loss, one abortion possibly treatment-related.
		-	20	64	LOEL for **developmental** toxicity = 64 mg/kg/day, based on 2 total litter resorptions, associated reduction in post-implantation loss, and reduced fetal body weights.

SPINETORAM

Species	Study Type, Exposure	Sex	(mg/kg/day) NOEL	(mg/kg/day) LOEL	Findings at LOEL and characteristic findings at higher dose levels
Rat	Chronic/ oncogenicity, 24 months	M	11	22	LOEL: Reduced body weights, thyroid follicular cell vacuolation. Increased aggregates of macrophages or histiocytes in mesenteric lymph nodes at 33 mg/kg/day.
		F	13	27	LOEL: Thyroid follicular cell vacuolation, increased incidence or degree of aggregates of macrophages or histiocytes in mesenteric and mediastinal lymph nodes. Increased bilateral retinal vacuolation (very slight to slight degree) at 40 mg/kg/day.
Mouse	Oncogenicity, 18 months	M	19	38	LOEL: Hyperplasia and inflammation of stomach glandular mucosa, vacuolation of epididymides.
		F	24	47	LOEL: Hyperplasia and inflammation of stomach glandular mucosa, decrements in body weight and food consumption.
Dog	Chronic, 12 months	M	3.0	≈5	LOEL: arteritis above background degree in one of 4 males, noted bilaterally in epididymides, considered treatment-related.
		F	2.5	≈5	LOEL: arteritis above background degree in one of 4 females, noted in larynx, thymus, thyroid, urinary bladder: considered treatment-related.
Rat	Reproduction, two generation	M	10	≈75	LOEL: Fine, diffuse cytoplasmic vacuolation in thyroid follicular epithelial cells, 2/54 males with very slight yellow-brown "lipofuscin-like" pigmentation in kidney proximal tubular epithelial cells.
		F	10	≈75	LOEL: Fine, diffuse cytoplasmic vacuolation in thyroid follicular epithelial cells, 20/54 females with very slight yellow-brown "lipofuscin-like" pigmentation in kidney proximal tubular epithelial cells.
		(F)	10	≈75	**Reproductive Effects** LOEL: dystocia in a few dams of both generations.
		(F)	75	N/A	**Pup growth and viability** NOEL = highest dose tested (no effects)
Rat	Developmental Toxicity	F	100	300	**Maternal** toxicity based on decreased body weight gain and food consumption.
		-	300	N/A	NOEL for **developmental** toxicity = highest dose tested.
Rabbit	Developmental Toxicity	F	10	60	LOEL for maternal toxicity was based on decreased body weight gains, decreased food consumption, decreased fecal output, and perineal soiling. Treatment was uniformly lethal to does at 100 mg/kg/day and above.
		-	60	N/A	LOEL for **developmental** toxicity = highest dose with surviving does.

SPIROTETRAMAT

Species	Study Type, Exposure	Sex	(mg/kg/day) NOEL	(mg/kg/day) LOEL	Findings at LOEL and characteristic findings at higher dose levels
Rat	Chronic/ oncogenicity, 24 months	M	12.5	169	LOEL: dilatation of renal tubules in kidney outer medulla. At 373 mg/kg/day, males had 10% body weight reduction, and increased exfoliated or immature germ cells in epididymides.
		F	16.8	229	LOEL: dilatation of renal tubules in kidney outer medulla. At top dose of 823 mg/kg/day, females showed a 14% body weight decrement, scaly skin, and perianal yellow or brown staining.
Mouse	Oncogenicity, 18 months	M	263	1022	LOEL: Two rare, benign subcutaneous tumors at 1022 mg/kg/day, compared to none in other groups, were possibly treatment-related. There was no associated histopathology.
		F	1319	N/A	NOEL = highest dose tested.
Dog	Chronic, 12 months	M	N/A	6	All treated groups had altered thyroid-associated hormone changes, such as decreased thyroxin at 6 to 55 mg/kg/day. At the highest dose, 2 males showed reduced size of follicles. One of these showed clinical signs which may have been related to thyroid deficiency, such as "ataxia," "decreased activity," "unsteady," and "lying on side.
		F	N/A	5	All treated groups had altered thyroid-associated hormone changes, such as decreased thyroxin at 5 to 48 mg/kg/day. There was no associated histopathology, nor were there clinical signs.
Rat	Reproduction, two generation	M	19	80	Systemic LOEL, based on decreased kidney weights in F1 males. Highest dose findings (419 mg/kg/day) were reduced body weights and a high incidence of kidney tubular dilatation (chiefly at the outer portion of the medulla) in F1 males.
		F	90	540	Systemic LOEL: Highest dose findings were reduced body weights and a high incidence of kidney tubular dilatation (chiefly at the outer portion of the medulla), each in F1 females.
		(M)	71	419	**Reproductive Effects** LOEL in males based on abnormal spermatozoa in one 6000 ppm male.
		(F)	485	N/A	**Reproductive Effects** NOEL = 485 mg/kg/day (no effects at highest dose).
		(F)	82	485	**Pup growth and viability** LOEL based on reduced pup body weight gain (both generations).
Rat	Developmental Toxicity	F	140	1000	LOEL based on decreased body weight and decreased food consumption.
		-	140	1000	LOEL based on decreased fetal weight and fetal ossification delays.
Rabbit	Developmental Toxicity	F	10	40	LOEL for **maternal** toxicity based on one doe which aborted. At the highest dose (160 mg/kg/day), there were 2 abortions and 6 of the 30 does with premature deaths or moribund sacrifices.
		-	10	40	LOEL is based on the variation "distinct liver lobulation." This was observed in 2 fetuses (1 litter) at 40 mg/kg/day, and in 8 fetuses (2 litters) at 160 mg/kg/day.

THIAMETHOXAM

Species	Study Type, Exposure	Sex	(mg/kg/day) NOEL	(mg/kg/day) LOEL	Findings at LOEL and characteristic findings at higher dose levels
Rat	Chronic/ oncogenicity, 24 months	M	21	≈60	LOEL: Increased incidence and/or grade of kidney lymphocytic infiltration and of chronic nephropathy at the highest dose tested.
		F	50	≈150	LOEL: Increased incidence and/or grade of foci of hepatocellular alteration, particularly clear cell subtype, at the highest dose tested.
Mouse	Oncogenicity, 18 months	M	2.6	≈65	LOEL: Hepatocellular adenomas, associated with hepatocellular hypertrophy, necrosis of single hepatocytes, and infiltration of inflammatory cells. Increased hepatocellular adenoma multiplicity and hepatocellular adenocarcinomas were observed at about 160 mg/kg/day and above, and increased hepatocellular mitotic activity was observed in this range. Splenic extramedullary hematopoiesis and glandular stomach epithelial hyperplasia of the gastric mucosa were observed at about 320 mg/kg/day.
		F	3.7	≈90	LOEL: Hepatocellular adenomas, associated with hepatocellular hypertrophy, necrosis of single hepatocytes, and increased hepatocellular mitotic activity. Increased hepatocellular adenoma multiplicity and hepatocellular adenocarcinomas were observed at about 225 mg/kg/day and above. Splenic extramedullary hematopoiesis and glandular stomach epithelial hyperplasia of the gastric mucosa were observed at about 450 mg/kg/day.
Dog	Chronic, 12 months	M	4.0	≈20	LOEL: Testicular tubular atrophy, bilateral, in 2/4 dogs of the two highest dose groups, at about 20 and 40 mg/kg/day, respectively. Absolute and relative testis weights were reduced at about 40 mg/kg/day.
		F	4.5	≈22	LOEL: Increases in plasma creatine and urea and albumin levels were reduced in females over the range of about 22-44 mg/kg/day.
Rat	Reproduction, two generation	M	3.7	75	Systemic LOEL: Hyaline droplets and hyaline casts in F1 male kidneys.
		F	209	N/A	Systemic LOEL: No systemic effects up to highest dose tested.
		(M)	75	192	**Reproductive Effects** LOEL is based on "germ cell loss/disorganization and/or Sertoli cell vacuolation," usually "minimal" degree, in F1 males.
		(F)	209	N/A	**Reproductive Effects** NOEL is the highest dose tested (no effects).
		(F)	209	N/A	**Pup growth and viability** LOEL = highest dose tested (no effects in either generation).
Rat	Developmental Toxicity	F	30	200	LOEL for **maternal** toxicity is based upon diminished body weight gain and diminished food consumption. At 750 mg/kg/day, 17 dams had dose-related hypoactive behavior, piloerection and regurgitation of test material, and one died. Food consumption for high dose dams during dosing period was only about 55% of controls.
		-	200	750	LOEL for **developmental** toxicity is based on decreased fetal body weight (10% decrement) and skeletal variations, mainly ossification delays.
Rabbit	Developmental Toxicity	F	15	50	LOEL for **maternal** toxicity based on reduced body weight gain. Food consumption at 50 and 150 mg/kg/day during days 7-12 was 78% and 24% of controls, respectively.
		-	50	150	LOEL for **developmental** toxicity based on increased early resorptions, marked decrease in fetal body weights, modest delayed ossification and small increases in minor skeletal anomalies.

CONCLUSIONS

Control of the Asian citrus psyllid is a high priority in California. Current efforts to eliminate isolated populations consist of a combination of immediate-acting foliar treatments and longer lasting systemics, the latter being applied as soil drench or foliar sprays per product directions. There are several classes of chemical controls, to guard against resistance. This presentation addresses toxicity profiles of the five most recently registered pesticides among the 13 active ingredients proposed by the UC IPM program in 2011. These five active ingredients have relatively low toxicity. This, coupled with the relatively low application rates for the five chemicals, suggests that it is unlikely that any of these treatments will pose significant health hazards.