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REVIEW ARTICLE

Managing resistance is critical to future use of pyrethroids and neonicotinoids

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Synthetic pyrethroids and neonicotinoids are the most readily available alternatives to the organophosphate and carbamate insecticides. Pyrethroids have become widely used in California, and problems with insecticide resistance and nontarget impacts have already been identified. Neonicotinoids are a new class of insecticide with uses only now being realized. Managing insecticide resistance will be crucial to preserving these new materials as organophosphate uses are lost.

Neonicotinoid and pyrethroid insecticides have become important replacements for organophosphates. UC Riverside staff research associate Greg Ballmer uses a micropipette to extract xylem from a grapevine in the Temecula Valley.

Insecticides are often referred to as having a broad or narrow spectrum of activity, depending on the diversity of pest species they kill. Narrow-spectrum insecticides are generally thought of as being less disruptive to biological control and more environmentally benign because of their specificity to a few target pest species. In the presence of a complex pest community, however, use of an insecticide with a high degree of specificity can require additional applications of products that target other taxa.

The ability of organophosphate (OP), organochlorine and methyl carbamate insecticides to control a broad range of insects with a single application led to their widespread use for pest control. With the cancellation of DDT by the U.S. Environmental Protection Agency in 1973, followed by bans on the use of most other organochlorines, agricultural use of the OP and methyl carbamate insecticides became dominant, with more than 200 OP insecticides available worldwide at their peak.

OPs and methyl carbamates are still widely registered for use on California crops and have been regarded as especially important tools for growers of vegetable and fruit crops, which are unique and economically important components of California's agricultural industry. California Department of Pesticide Regulation (DPR 2003) reports of OP usage for 2002 (the most recent data published) indicate that chlorpyrifos, diazinon and malathion are the most widely used OPs, while methomyl and carbaryl are the only two methyl carbamates used to any great extent (table 1).

The widespread use of these products has led to the development of pesticide resistance in many insect populations (Roush and Tabashnik 1990). Their use has also raised concerns about surface-water contamination, resulting in the listing of some California rivers as impaired waterways under the U.S. Clean Water Act. The U.S. Food Quality Protection Act (FQPA) of 1996 has focused particular attention on the human risks of exposure to OPs and has already imposed restrictions on their use (see page 7).

In a recent report funded by the California Department of Food and Agriculture (Metcalfe et al. 2002), pyrethroid and neonicotinoid insecticides were identified as the most likely alternatives to the OPs. Even before the OPs are withdrawn, however, the number of applications of

TABLE 1. Usage of organophosphate and methyl carbamate insecticides in California, 2002

Chemical (trade name)	Pounds a.i.* applied	No. applications
Organophosphates		
Chlorpyrifos (Lorsban)	1,446,547	36,802
Diazinon	689,603	31,757
Malathion	619,811	14,653
Phosmet (Imidan)	405,088	7,533
Dimethoate (Cygon)	332,543	24,355
Methyl carbamates		
Methomyl (Lannate)	321,476	17,216
Carbaryl (Sevin)	256,030	3,354

* Active ingredient.
Source: DPR 2003.

these alternative insecticides is fast approaching that of the OPs in California agriculture (table 2). This is alarming, because it suggests that application of these materials will continue to increase, raising immediate concerns about the potential development of resistance.

Although non-OP alternatives are already available for most crops, phasing out the OPs will require some adjustment to current management programs as suitable replacements among the remaining insecticide classes are sought. Pyrethroids are fast-acting insecticides that kill a broad spectrum of insect pests. They are most often applied as foliar sprays, by air or ground. For a number of crop uses, they are serving as a direct substitute for an OP. All currently registered neonicotinoids in California agriculture are available as foliar formulations and compare favorably with the OPs in terms of efficacy against specific groups of insect pests, impacts on natural enemies, and worker and environmental safety.

Pyrethroids increasingly popular

Pyrethroid insecticides are more stable analogs of the natural insecticides found in extracts from Chrysanthemum flowers *(Tanacetum [Chrysanthemum] cinerariaefolium)*. Research to develop synthetic pyrethroids began in the 1940s to enhance their efficacy, facilitate large-scale production and improve stability. Allethrin (Pynemin) was the first synthetic pyrethroid to be developed and was registered in 1949 for public health and urban uses, primarily against mosquitoes and houseflies. This was considered a first-generation pyrethroid, because it was chemically similar to a component of the natural pyrethrum extract.

Second-generation pyrethroids were registered in the 1960s to control urban insects. Resmethrin was about 20 times more effective than pyrethrum for controlling houseflies and had longer residual activity, but like allethrin was photolabile (containing molecules that break down quickly in light) and therefore unsuitable for outdoor use. Permethrin was the first synthetic pyrethroid with sufficient photostability for agricultural applications.

TABLE 2. Usage of synthetic pyrethroid and neonicotinoid insecticides in California, 2002

Chemical name	Pounds a.i.* applied	No. applications	Common agricultural uses
Pyrethroids			
Bifenthrin	47,443	5,646	Cotton, corn, strawberry, alfalfa
Cyfluthrin	57,524	10,258	Alfalfa, cotton, orange, corn
Cypermethrin and (s)-cypermethrin	306,291	8,326	Lettuce, cole crops, onion, cotton
Deltamethrin	13,001	956	Greenhouse, nursery
Esfenvalerate	30,758	24,623	Almond, cotton, artichoke, stone fruit
Fenpropathrin	34,525	4,012	Cotton, grape, strawberry, orange
Lambda-cyhalothrin	58,381	22,642	Alfalfa, lettuce, rice, tomato
Permethrin	385,403	46,267	Lettuce, celery, spinach, almond
Neonicotinoids			
Acetamiprid	6,632	3,519	Cotton, lettuce, celery, pear
Imidacloprid	224,730	41,924	Lettuce, grape, cotton, cole crops
Thiamethoxam	11,091	2,826	Cotton, tomato, melon, pepper

* Active ingredient.
Source: DPR 2003.

Permethrin and fenvalerate became the most widely used of the third-generation pyrethroids and were particularly significant for their broad spectrum of insecticidal activity at relatively low rates, as well as their improved photostability, which resulted in residual activity of up to 1 week on foliage. Permethrin (Pounce or Ambush) is still the most widely used pyrethroid in California, and is commonly applied to leafy vegetables and some tree crops.

A number of fourth-generation pyrethroids have been registered during the past 20 years, the most commonly used being esfenvalerate (Asana) and lambda-cyhalothrin (Warrior or Karate). Because they are more effective against insects at lower dosages than the third-generation pyrethroids, these contemporary pyrethroids are generally applied at much lower rates (typically 10% of the third-generation rates). The fourth-generation pyrethroids are photostable and relatively nonvolatile, so their residual activity is longer than that of earlier pyrethroids.

Top, **UC Riverside extension entomologist Nick Toscano examines a Coachella Valley grapevine trunk for adult and nymph populations of vine mealybug, part of a field trial of various treatments. *Above,* vine mealybug damages grapevines, causing them to lose vigor and diminishing grape quality.**

Efficacy and cost. Pyrethroids have become the favored insecticide alternatives to the OPs for growers because in many cases, they are a direct substitute in terms of the range of insects killed, treatment timing and residual activity. Perhaps the only arthropod groups for which they are not as effective are soil insects and mites, and certain insects with piercing-sucking mouthparts. The availability of pyrethroids continues to increase as more products are registered for additional California crops, including fruits and vegetables. In general, they are cost-competitive as a direct substitute for the OPs and in some cases are even less expensive.

Toxicity. In addition to efficacy and cost, pyrethroids present a lower risk to workers and applicators, as indicated by oral and dermal LD_{50} data (table 3). LD_{50} is the dose that kills 50% of test animals to which a product is administered and is expressed as milligrams per kilogram of body weight. Pyrethroid toxicity to amphibians, mammals and birds is relatively low compared to the OPs;

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however, most aquatic invertebrates and fish are highly susceptible (Smith and Stratton 1986). Acute toxicity expressed as 96-hour LC_{50} values (the concentration lethal to 50% of a group of organisms within 96 hours) for esfenvalerate to juvenile fish was reported at 0.25 micrograms per liter ($\mu g/L$)(Werner et al. 2002), while the respective 96-hour LC_{50}s of diazinon are as much as 1,000-fold higher (EXTOXNET 2003). Molluscs are relatively insensitive to both OPs and pyrethroids, but have been shown to bioaccumulate these chemicals, thereby representing a potential hazard to higher trophic levels within the food chain.

Water quality. The off-site movement of pyrethroids, a concern with the OPs in California surface waterways, is generally believed to be minimal due to their hydrophobic chemical properties and generally high soil-adsorption coefficients, which indicate that they will bind to surfaces they come into contact with rather than run off. However, data has recently been collected that found permethrin, esfenvalerate, bifenthrin and lambda-cyhalothrin in 75%, 32%, 25% and 12%, respectively, of sediment samples taken from surface-water bodies in California's Central Valley (Weston et al. 2004). With increases in pyrethroid use likely, this may prove to be problematic in the future (see page 5).

Secondary pests. Beneficial insects and mites are an important component of integrated pest management (IPM) since they can reduce the need for insecticides when present at sufficient densities. Pyrethroids have been shown to seriously affect beneficial arthropods present in agricultural crops, and they are generally not compatible with biological control programs. They also tend to persist for longer periods in the environment and can be especially disruptive when used in perennial crops. Pyrethroid use has been associated with outbreaks of secondary pests such as spider mites in orchards both during the season in which they are applied and possibly in subsequent seasons (Bentley et al. 1987). This will lead to increased use of miticides and other chemical pesticides in order to control these outbreaks.

Neonicotinoids more selective

There are four neonicotinoid insecticides (synthetic chemicals based on the structure of nicotine) currently registered for agricultural use in California — acetamiprid (Assail), imidacloprid (Admire or Provado), thiacloprid (Calypso) and thiamethoxam (Platinum or Actara). Nitenpyram is registered in California for flea control in cats and dogs. Others are under development.

Imidacloprid was introduced in 1991 as the first commercially available neonicotinoid and is by far the most widely used (table 2). Like all neonicotinoids, it is a remarkably potent neurotoxic insecticide, which acts as a nicotinic acetylcholine receptor agonist. The target-site selectivity of imidacloprid and other neonicotinoids is a major factor in their favorable toxicological properties because they act at much lower concentrations in insects than in mammals. Imidacloprid was developed from nithiazine, a heterocyclic nitromethylene that was first reported in 1978. Although it exhibited considerable insecticidal activity, nithiazine was not made commercially available due to its photolability.

Efficacy and cost. The efficacy of the neonicotinoids both as persistent systemic treatments and as less-persistent foliar sprays offers exceptional flexibility that is similar to that of some OPs. For example, imidacloprid is currently available for systemic, seed, soil, chemigation (applied via the irrigation system) and foliar applications. The systemic activity of neonicotinoids enables their integration into California agriculture as a satisfactory alternative to the OPs for the control of sucking insects, as well as some Coleoptera (beetles) and Diptera (flies). However, the neonicotinoids will not control some insect orders — such as the Lepidoptera — as effectively as the OPs, preventing their direct substitution for OPs and pyrethroids in many cases. This characteristic of neonicotinoids is good for resistance management in that growers must utilize other available chemistries for some species rather than relying solely on one insecticide class for controlling all insect pests. One limitation is their cost, which tends to be much higher than either OPs or pyrethroids.

Toxicity. Neonicotinoids share with the pyrethroids a relatively low risk of dermal toxicity to mammals (table 3), and their oral LD_{50}s make them suitable for use on fruit and vegetable crops. As their registered crop uses expand on California's "minor use" or "specialty" crops (generally those grown on 300,000 acres or less), they will likely replace many OPs. Where they have already been registered, such as on lettuce and cole crops, their use is well established (table 2).


Jack Kelly Clark

Left, **xylem is placed in a pressure bomb and will later be tested in the UC Riverside laboratory for neonicotinoid insecticides that kill the glassy-winged sharpshooter, *center.* The insect carries the pathogen that causes Pierce's disease, which has killed vines in the Temecula Valley, *right.***

Top: ***left,*** **UC Riverside postgraduate researcher Jian Bi catalogues peppers for an efficacy study of various alternatives to organophosphate insecticides, including neonicotinoids, pyrethroids, insect growth regulators and organic products;** ***right,*** **Ballmer collects insects using a suction sampler. Bottom:** ***left,*** **an adult potato psyllid;** ***right,*** **psyllid damage to a red pepper.**

Water quality. Neonicotinoids are more similar to OPs than pyrethroids in their potential to move through the soil and run off in surface water. The California Pollution Contamination Prevention Act of 1985 established a set of specific numerical values (SNV) for pesticides and required DPR to place active ingredients on a list of candidates as potential leachers if their water solubility value exceeds 3 parts per million (ppm) or if the soil adsorption coefficient is less than 1,900 cm^3/g, and if one of three persistence parameters is exceeded. The three major neonicotinoids currently registered in California all exceed the SNVs and are on the list, suggesting that care is needed when using these products to protect water quality.

Imidacloprid is soluble in water (5.14 g/l), has moderate binding affinity to organic materials in soils ($K_{oc} = 262$) and a relatively long half-life in soils (365 days). Acetamiprid is also water-soluble (2.95 g/l), has similar binding affinity to organic materials in soils ($K_{oc} = 260$), but is short-lived in soils (1 to 8 days). Thiamethoxam is water-soluble (3.26 g/l), but has low binding affinity to organic materials in soil (K_{oc} = 43 to 77) and is more persistent (385 to 408 days) than the others. Soil type and irrigation practices will therefore be important considerations for growers in order to optimize neonicotinoid efficacy while preventing possible unwanted environmental effects.

Nontarget organisms. The impacts of neonicotinoids on nontarget organisms remain unclear. For example, there is some controversy over the safety of systemic treatments to both natural enemies and bees that may encounter neonicotinoid residues in nectar and pollen (Schmuck et al. 2001). This is a current area of research to better define specific risks and evaluate mitigation measures if necessary.

Pest resistance is a major concern

The effective deployment of new insecticides within pest management programs should include strategies for delaying the development of pest resistance. The two most common mechanisms conferring resistance to the OP and pyrethroid insecticides are target-site insensitivity and detoxification. Target-site insensitivity arises from a reduced binding between the insecticide and its intended target. The OPs bind to and inhibit the activity of the synaptic enzyme acetylcholinesterase (AChE), resulting in the disruption of the normal transmission of nerve impulses across the synapse. In resistant insects, insensitivity of the AChE to binding by the OP restores synaptic function even in the presence of the OP.

Pyrethroids bind to sites on the sodium channel and in so doing disrupt the transmission of impulses along the nerve axon by holding the channels in an open position (Bradbury and Coats 1989). Pyrethroid resistance occurs when mutations in sodium channel genes reduce the capacity of the pyrethroids to bind effectively, thereby enabling the channels to function normally. Currently, there is no evidence for target-site resistance in neonicotinoids. This is important because target-site resistance can act as a foundation upon which other resistance mechanisms develop. These in turn can disrupt management programs due to cross-resistance to other insecticide classes.

Cross-resistance occurs in an insect when a resistance mechanism selected for in response to exposure to one insecticide also confers resistance to a second insecticide to which the insect has not been exposed. Target-site cross-resistance is very common within individual insecticide classes due to the similarity in binding sites. However, cross-resistance between insecticide classes having different modes of action is viewed as a more serious problem, because insecticides to which an insect has previously been unexposed may be jeopardized through the selective forces of an unrelated insecticide. This can have a serious impact on the development of pest management strategies, particularly when emergency registrations of new insecticides are under consideration as potential control agents. Detoxification mechanisms are an extremely important source of cross-resistance between insecticides that differ in their target sites. There are three broad groups of detoxification enzymes — the carboxy-

TABLE 3. Oral and dermal toxicities of commonly applied insecticides on California crops*

Chemical name	Oral LD_{50} rat; mg/kg	Dermal LD_{50} rabbit; mg/kg
Organophosphates		
Chlorpyrifos	96–270	2,000
Diazinon	1,250	2,020
Dimethoate	235	400
Pyrethroids		
Esfenvalerate	458	> 2,000
Lambda-cyhalothrin	1,593	> 2,000
Permethrin	430–4,000	> 2,000
Neonicotinoids		
Acetamiprid	1,064	> 2,000
Imidacloprid	> 4,870	> 2,000
Thiamethoxam	> 5,000	> 2,000

* Higher LD_{50} values indicate lower oral or dermal toxicity.

Photos: Jack Kelly Clark

Left, **pyrethroids can be disruptive of natural enemies, such a the western orchard predator mite.** ***Right,*** **whiteflies are often the target of neonicotinoid applications.**

lesterases, the cytochrome P450s and the glutathione-S-transferases — and each of these has been implicated in resistance to the OPs and pyrethroids.

Unfortunately, resistance to pyrethroids has already been reported for a number of insect species in California and elsewhere. The neonicotinoids, however, are relatively new to California agriculture, and there has yet to be a substantiated case of resistance arising from their application under field conditions. Continuous laboratory selection of a whitefly population collected from melon crops in the Imperial Valley resulted in 80-fold resistance to imidacloprid, illustrating that resistance genes are present in California whiteflies. Resistance has been documented in field populations of the silverleaf whitefly *(Bemisia)* in Arizona and worldwide in Spain, Israel and Guatemala (Byrne et al. 2003). In the northeastern United States, resistance to imidacloprid was detected in the Colorado potato beetle *(Leptinotarsa decemlineata)* just 2 years after its initial use (Zhao et al. 2000).

The OPs are occasionally used in mixtures with pyrethroids to synergize their activity. The synergistic effect is believed to occur when the OPs inhibit pyrethroid-hydrolyzing esterases, thereby enabling toxic doses of the pyrethroid to accumulate at the target site. Mixtures of the OP acephate (Orthene) and the pyrethroid fenpropathrin (Danitol) were used effectively for whitefly control on cotton, although in recent years reliance on this strategy has suffered due to the development of target-site resistance to the pyrethroid, a mechanism that is not synergizable by the OP. In Arizona, a resistance management strategy was introduced in 1996 to combat whitefly resistance problems. A strategy of incorporating insect growth regulators (IGRs), pyrethroids and nonpyrethroid conventional insecticides in a multistage program proved successful, as documented by a dramatic reduction in the total number of pesticide applications (Ellsworth 1998) and the restoration of susceptibility to synergized pyrethroids and nonpyrethroids (Dennehy et al. 1997).

Delaying the onset of resistance

The ultimate impact to California agriculture of losing OP insecticides will depend very much upon how alternative insecticides are deployed. Perhaps the most immediate insect-control problem for California agriculture will not be finding a suitable replacement for the OPs as insecticides, but rather to delay the onset of and manage pest resistance to the pyrethroids and neonicotinoids that are replacing them.

The pyrethroids have an established history of use in California and much is known about their efficacy as pest control agents, as well as their negative impacts on nontarget species and the environment. They are prone to resistance, and a concern is that they may face additional problems with resistance without their OP synergists. By contrast, the neonicotinoids are a new class of insecticide and their influence in pest control is only now being realized as new products are developed and new uses identified. There is no evidence of resistance to neonicotinoids at present in California agriculture, although resistance has been documented elsewhere. It will be necessary for growers and pest management specialists to use both classes of materials judiciously and in combination with other alternatives as feasible, to avoid resistance problems and maintain environmental quality.

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