Predicting the Activity of Soil-Applied Insecticides from Their Physicochemical Properties

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The influence of physicochemical properties on the activity of soil-applied insecticides is discussed. Physical property-based rules are developed which allow prediction of the soil activity of an insecticide against the larvae of southern corn rootworm (*Diabrotica undecimpunctata howardi*) from its topical potency, lipophilicity, and volatility. These rules, developed from measurements with 16 pyrethroids, predict the soil activity of non-pyrethroid insecticides within a 6-fold accuracy. The finding that physical properties of an insecticide can significantly affect its soil activity suggests that selection of compounds for advanced evaluations should be based on these properties as well as the level of potency.

INTRODUCTION

Numerous papers have addressed the impact of varying soil and environmental conditions on the efficacy of soil insecticides (Edwards, 1966; Harris, 1972; Harris and Bowman, 1981; Felsot and Lew, 1989). Edwards was concerned primarily with understanding the residual behavior of the chlorinated hydrocarbon insecticides in soil and concluded that the volatility and water solubility of the insecticide were the principal determinants of residual behavior (Edwards, 1966). Harris reviewed the factors which influence the effectiveness of soil insecticides and indicated that, in addition to environmental factors, the properties of the insecticide were important determinants of soil efficacy (Harris, 1972). Relationships have been established between water solubility and toxicity in soil for a series of phosphate insecticides. In fact, Harris and Bowman concluded that a highly toxic contact insecticide could be a poor soil insecticide if its water solubility was too high (Harris and Bowman, 1981). Recent work has shown that soil organic carbon content was the single most significant determinant of soil efficacy for carbofuran and terbufos (Felsot and Lew, 1989). Most of the historical work has focused primarily on understanding how changes in soil characteristics affect the toxicity of soil-applied commercial insecticides. While informative, this perspective does not readily facilitate the process of discovering new chemistries with optimal soil efficacy. Since optimal properties of an agrochemical can be designed into the molecule during the discovery process, the potentially more useful perspective is the converse: How does variation in the physical properties of insecticides affect their performance in soil?

As part of an ongoing effort directed at understanding the role of physical properties on the efficacy of soil-applied agrochemicals, a model has been developed regarding the translation of laboratory topical potency against southern corn rootworm larvae (*Diabrotica undecimpunctata howardi*) into soil activity for a series of pyrethroids. This work parallels our earlier work which focused on understanding which physical properties of a series of herbicides influence their soil efficacy (Simmons et al., 1992). The finding that lipophilicity and volatility significantly influence the soil efficacy of these experimental herbicides underscores the fact that soil bioavailability is governed by an agrochemical's overall physical properties and is independent of its mode of action. Similar observations and conclusions have been drawn previously (Briggs, 1984).

MATERIALS AND METHODS

Biological Evaluations. *Insect Rearing.* The larvae used in this study were obtained from a laboratory colony at FMC and reared according to literature methods (Jackson, 1985).

Topical Bioassay. The intrinsic toxicity of compounds to larvae was determined by topical bioassay as described in the literature (Ball et al., 1975). Third-instar larvae were topically treated with 1 μL of an acetone solution of the technical grade insecticide applied to the thoracic dorsum of each larva. The larvae were exposed to a minimum of five concentrations of each insecticide with at least 20 larvae per concentration replicated twice. Acetone controls were included in all tests. Control and treated larvae were held at 25 °C and 50% relative humidity in 9-cm Petri dishes lined with filter paper moistened with water and containing two corn sprouts as food. Mortality was determined 48 h after treatment. Dose–mortality responses were analyzed by probit analysis to afford an LD_{50}, reported in units of micrograms per gram of body weight.

Soil Bioassay. Concentration–mortality responses of second-instar larvae were determined in a silt loam soil from Champaign, IL, with 1.8% organic matter content. Soil pH at this site was 6.4, with a soil composition consisting of 21% clay, 27% sand, and 52% silt, with an overall cation-exchange capacity (CEC) of 9.8 (Sutter, 1982; Lew and Sutter, 1985). The appropriate insecticide dosage was dissolved in acetone and added to a sufficient amount of water to adjust the soil moisture level to 20% (w/w). This moisture level compares favorably to the moisture level of this soil under typical field conditions, the field capacity for this soil being 29% (w/w). Before infestation with larvae, the treated soil was thoroughly mixed. Two or three replicates of 10 larvae were used at each concentration. Although infested on the surface of the soil, the larvae moved into the soil very quickly thereafter. At least five concentrations and an untreated control were used to estimate the concentration–mortality responses. After incubation at 25 °C for 3 days under a 12 h/12 h dark/light photoperiod, the number of dead or alive larvae was determined using a modified Berlese funnel technique (Sutter, 1982). Concentration–mortality responses were analyzed using probit analysis to afford an LC_{50}, reported in units of micrograms per gram of soil.

Selection of Chemical Analogs. The 16 analogs (Chart I) were selected to represent structural variations in the acid portion, the "alcohol" portion, and the linkage of the pyrethroid, as well as to represent a wide range in lipophilicity, volatility, and topical potency against larvae. The lipophilicity for each analog was estimated using the Medchem *C* log *P* program (version 3.33 from A. Leo and D. Weiniger, Pomona College). Vapor pressures were estimated using a proprietary computer program which

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0021-8561/92/1440-1432$03.00/0

Chart I

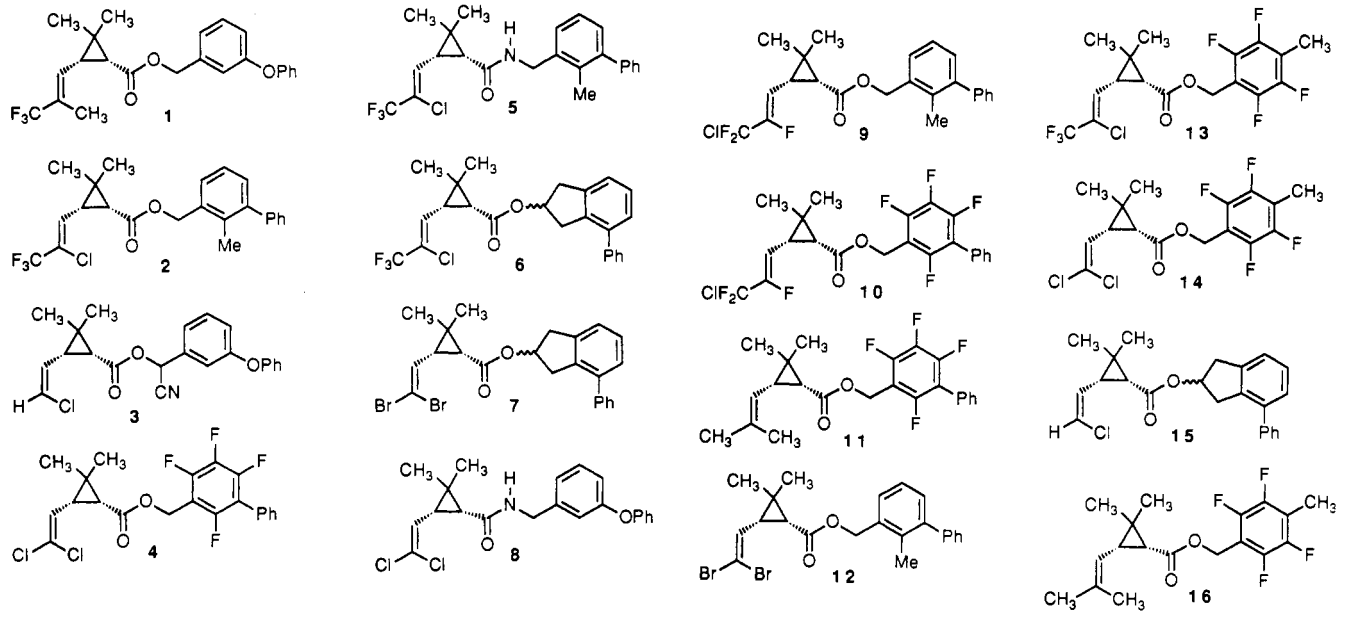


Table I. Physical Characterization of New Pyrethroids

compd	mp, °C	molecular formula	anal. (C, H, N), calcd/found	^{1}H NMR ($CDCl_3$), δ multiplicity[a] (area)
5	oil	$C_{23}H_{23}ClF_3NO$	65.48/65.38, 5.50/5.68	1.25 s (3 H), 1.40 s (3 H), 1.60–2.10 m (2 H), 2.22 s (3 H), 4.50 d (2 H), 5.95 br m (1 H), 7.10–7.50 m (9 H)
9	oil	$C_{23}H_{22}ClF_3O_2$	M$^+$ 422.1278/422.1260	1.35 s (6 H), 2.0–2.2 m (2 H), 2.30 s (3 H), 5.25 s (2 H), 6.15 dd (1 H), 7.2–7.5 m (8 H)
11	oil	$C_{23}H_{22}F_4O_2$	67.97/67.78, 5.46/5.64	1.18 s (3 H), 1.25 s (3 H), 1.68 s (3 H), 1.67 m (1 H), 1.75 s (3 H), 1.90 t (1 H), 5.20 AB d (2 H), 5.35 d (1 H), 7.4–7.5 m (5 H)
15[b]	oil	$C_{23}H_{23}ClO_2$	75.30/75.28, 6.32/6.10	trans 1.18 s (3 H), 1.20 s (3 H), 1.50 m (1 H), 2.00 m (1 H), 3.10–3.15 m (2 H), 3.35 br d (2 H), 5.50 br s (1 H), 5.55–5.65 m (1 H), 6.00–6.10 dd (1 H), 7.20–7.45 m (8 H) cis 1.23 s (3 H), 1.25 s (3 H), 1.50 m (1 H), 2.37 m (1 H), 3.00–3.10 m (2 H), 3.42 br d (2 H), 5.40–5.45 m (1 H), 5.50 br s (1 H), 6.10–6.15 m (1 H), 7.20–7.45 m (8 H)
16	oil	$C_{18}H_{20}F_4O_2$	M$^+$ 344.1419/344.1399	1.15 s (3 H), 1.22 s (3 H), 1.63 d (1 H), 1.70 s (3 H), 1.75 s (3 H), 1.90 t (1 H), 2.25 s (3 H), 5.13 d (1 H), 5.18 d (1 H), 5.35 d (1 H)

[a] s, singlet; d, doublet; t, triplet; q, quartet; br, broadened; dd, doublet of doublets; dt, doublet of triplets; m, multiplet. [b] Compound 15 was a 35/65 mixture of cis/trans. The ^{1}NMR spectra are of the mixture and chemical shifts assigned to the cis and trans isomers.

calculates vapor pressure of agrochemicals from structural features. This program can estimate vapor pressures to within 2.5× accuracy across structurally diverse chemical classes which correspond to a vapor pressure range of 10^{15} mmHg. Vapor pressure estimates (C log V_p) are reported in log units (mmHg) at 25 °C and are considered reliable to ±0.40. Statistical analysis of the physical properties of the compounds in Chart I using factor analysis showed that lipophilicity, volatility, and topical potency were independently represented (Dixon, 1988).

Chemical Synthesis. The compounds shown in Chart I were prepared by standard methodology from known acids (Naumann, 1990). These acids were converted into the respective acid chlorides using oxalyl chloride in diethyl ether in the presence of a catalytic amount of dimethylformamide. Esterification (or amidation) with the appropriate alcohol (or amine) was performed in diethyl ether or tetrahydrofuran in the presence of 1 equiv of pyridine. The crude products were purified by column chromatography. All compounds were predominantly (>95%) of the cis configuration in the acid except for compounds 3 and 15, which consisted of a mixture of 35% cis and 65% trans. Except for compound 12, which was derived from the acid with the 1*R* configuration, all other acids were racemic mixtures. All chiral alcohols were also racemic mixtures as well. Configuration about the vinyl group in the acid is as drawn. Each new compound's structure was consistent with its ^{1}H NMR, IR spectrum, and elemental analysis (see Table I). Compounds 1–4, 6–8, 10, and 12–14 have been previously reported (DeSousa et al., 1982; Elliot, 1986; Elliot et al., 1988; Engel, 1982a, 1984; Plummer, 1983; Punja, 1981).

RESULTS AND DISCUSSION

Lipophilicity and volatility are recognized as influences on the performance of soil-applied agrochemicals as these properties dictate the distribution of a chemical between soil air and soil water (Figure 1) (Briggs, 1984; Graham-Bryce, 1981, 1984). Our goal was to understand how changes in lipophilicity and volatility for these analogs quantitatively influenced their performance in soil. The inherent assumption was that soil efficacy is primarily governed by the intrinsic toxicity of the analog, its ability to penetrate into the insect, and its bioavailability to the insect in the soil environment (eq 1). The bioavailability

$$\text{soil efficacy} = \underset{\text{(topical potency)}}{\text{intrinsic activity}} \times \text{penetration} \times \underset{(\log P,\ \log V_p)}{\text{bioavailability}} \quad (1)$$

of the chemical has two components. The first is availability to the insect due to initial placement in the soil. The second component of availability is that which is due to physical redistribution of the compound in the soil following initial placement. We view the second component as the more important of the two since a compound that has properties commensurate with good movement in the soil will potentially overcome a poor initial placement through this redistribution process.

We have chosen to utilize topical potency as the net measure of the compound's intrinsic activity and ability

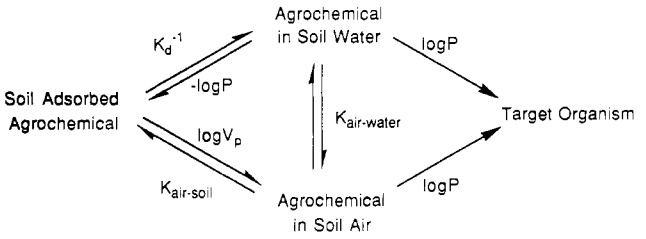


Figure 1. Equilibrium distribution of agrochemicals in soil. log P is the logarithm of the 1-octanol/water partition coefficient. log V_p is the logarithm of the vapor pressure.

Table II. Biological and Physical Data for Model Development

			Diabrotica			
			topical	soil pLC_{50}[b]		
compd	C log P	C log V_p	pLD_{50}[a]	obsd	predicted[c]	Δ
1	6.24	−6.85	−0.35	−0.48	0.21	−0.69
2	7.27	−7.55	0.57	0.66	0.70	−0.04
3	5.30	−7.94	−1.56	−1.24	−0.99	−0.25
4	7.17	−7.60	−0.91	−0.97	−0.78	−0.19
5	6.06	−11.17	−0.78	−1.06	−1.12	0.06
6	6.99	−7.87	−0.33	−0.40	−0.20	−0.20
7	7.34	−9.34	−1.07	−1.36	−1.37	0.01
8	5.60	−11.67	−1.22	−1.38	−1.55	0.17
9	7.21	−8.00	−0.37	−0.41	−0.33	−0.08
10	7.13	−7.39	−1.29	−1.02	−1.11	0.09
11	7.19	−6.56	−1.67	−1.35	−1.32	−0.03
12	7.63	−9.01	−0.42	−0.62	−0.72	0.10
13	5.96	−4.34	−0.56	0.82	0.63	0.19
14	5.93	−5.01	−0.52	1.00	0.53	0.47
15	6.21	−7.48	−1.16	−1.07	−0.74	−0.33
16	5.96	−3.97	−1.55	−0.32	−0.29	−0.03
average	6.57 ± 0.73	−7.61 ± 2.11				

[a] pLD_{50} is the negative logarithm of the dose (μg/g of larvae) required for 50% mortality. [b] pLC_{50} is the negative logarithm of the concentration (μg/g of soil) required for 50% mortality. [c] Using eq 5.

to penetrate into the insect. Since the evaluation time for the soil assay (3 days) was significantly shorter than the soil half-life for these compounds estimated from a soil bioassay ($t_{1/2} \geq 7.5$ days, data not shown), it was assumed that soil degradation of the pyrethroids to inactive metabolites during the time course of the assay could be disregarded.

Development of Translation Model. Biological and chemical data for the 16 analogs (Chart I) were collected into Table II. Using an all-possible regression technique to analyze the data, a statistical model was developed which correlated the observed soil efficacy to topical potency, C log V_p, and C log P for each analog. This regression technique creates all one-, two-, and three-parameter models from which the best model is selected (Draper and Smith, 1966; Purcell, 1973). The statistically best equation (eq 5) and its development (eqs 2–5) are presented (Table III). r^2 is the explained variance and is adjusted for the number of parameters in each equation, s the standard error of the regression equation, and F the value for the F statistic. All terms were significant to at least the 98% level based upon the Student t-test. Inclusion of each additional term was judged as significant by comparing r^2, s, and F to equations of fewer terms (Draper and Smith, 1966).

It is not surprising that topical potency is the most significant single property, explaining 40% of the observed variance in soil efficacy (eq 2). The second best single-parameter model (not shown) was based upon C log V_p (r^2 = 0.33). Inclusion of either C log P (eq 3) or C log V_p (eq 4) improves the model by increasing the explained variance

Table III. Development of Regression Models

pLC_{50} soil = A × pLD_{50} topical + B × C log V_p + C × C log P + D

A[a]	B	C	D	r^2	s	F	eq
0.87 ± 0.26			0.14	0.40	0.61	10.9	2
1.02 ± 0.27		−0.35 ± 0.22	2.59	0.46	0.58	7.4	3
0.88 ± 0.15	0.23 ± 0.04		1.93	0.80	0.35	31.6	4
1.01 ± 0.13	0.22 ± 0.04	−0.28 ± 0.11	3.82	0.86	0.29	32.6	5

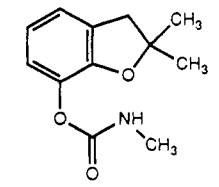
[a] A, B, C, and D are the corresponding regression coefficients for each term in the equation heading the table.

to 46% or 80%, respectively. However, inclusion of all three properties, topical potency, C log V_p, and C log P, provided the most statistically significant equation, which explained 86% of the observed variance in soil efficacy. By all statistical measures (r^2, s and F) eq 5 is of higher statistical significance than eqs 2–4 and is consistent with the physical processes portrayed in Figure 1. This model suggests that, for all other environmental factors being the same, greater soil efficacy would result from chemical analogs with enhanced volatility, reduced lipophilicity, and greater topical potency.

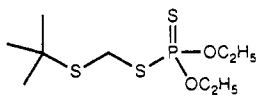
For the pyrethroids used to develop this model the average lipophilicity was 6.57 (range from 5.30 to 7.63) and the average volatility was 2.5×10^{-8} mmHg (range from 4.6×10^{-5} to 2.1×10^{-12} mmHg). As a general class the pyrethroids are too lipophilic and lack sufficient volatility for good bioavailability in soil. Figure 1 makes this clear. Because of their properties, the pyrethroids would be strongly adsorbed to the organic component of soil with little distribution into soil water or soil air; thus, little would be available for sorption into southern corn rootworm (the target organism). As the lipophilicity is lowered and the volatility raised, the distribution into these two phases would improve, with a resulting increase in bioavability. A particularly striking example can be seen in the comparison between bifenthrin and tefluthrin (Table II, cf. compounds 2 and 13). Despite being much less potent than bifenthrin (LD_{50} = 3.6 vs 0.27 μg/g), tefluthrin has superior soil efficacy (LC_{50} = 0.15 vs 0.21 μg/g) due to improved bioavailability, which results from its decreased lipophilicity and increased volatility.

Experiments were conducted in only one soil type. However, the described behavior is not unexpected given the generally observed behavior of agrochemicals in soil (Figure 1) (Briggs, 1984). We recognize that the derived model is dependent upon the specific characteristics of the soil used in the bioassay. However, this analysis clearly reveals that volatility and lipophilicity significantly affect an insecticide's soil activity. Although the magnitude of this effect could well vary across soil types, it seems likely that these properties would still prove significant. An interesting connection between our work and that of Chapman is that terbufos sulfoxide and carbofuran have very similar topical potencies against mole crickets [relative potency (molar) 1.0 vs 0.42, respectively], very similar physical properties (C log P 2.4 vs 2.5 and C log V_p −4.7 vs −4.7), and, as a result of these, very similar soil efficacies against mole crickets [relative ED_{50}s (molar) 1.0 vs 0.39]. This behavior is exactly in accordance with our model even though Chapman's study was conducted in a Plainfield sandy soil (5% moisture and 0.5% organic matter) (Chapman and Harris, 1980).

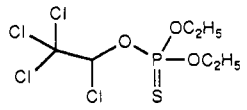
To explore the general applicability of this model, several commercial soil insecticides (Figure 2) were evaluated and their observed efficacies were compared to those predicted using eq 5 (Table IV). These compounds, which differ from the pyrethroids in mode of action, were not used in developing the model. However, in spite of the fact that their lipophilicity and volatility lie outside the range of



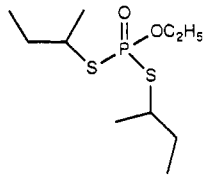
carbofuran



terbufos



DPX-43898



cadusafos

Figure 2. Commercial insecticides.

Table IV. Predicted Soil Efficacy of Several Commercial Soil Insecticides

			Diabrotica			
			topical	soil pLC_{50}[b]		
compd	$C \log P$	$C \log V_p$	pLD_{50}[a]	obsd	predicted[c]	Δ
carbofuran	2.47	−4.70	−1.20	0.70	0.88	−0.18
terbufos	3.86	−3.59	−0.21	1.22	1.74	−0.52
DPX-43898	5.84	−2.90	−0.02	1.52	1.53	−0.01
cadusafos	3.90	−3.05	−0.56	0.72	1.49	−0.77

[a] pLD_{50} is the negative logarithm of the dose (μg/g of larvae) required for 50% mortality. [b] pLC_{50} is the negative logarithm of the concentration (μg/g of soil) required for 50% mortality. [c] Using eq 5.

the pyrethroids used to derive eq 5, their soil efficacies are reasonably well predicted by this model. For the four examples, the two best predicted, carbofuran and DPX-43898, have one of two properties ($C \log P$, $C \log V_p$) within the range used to define the model. The two worst predicted, terbufos and cadusafos, have both properties outside this range.

Since most of these compounds have lower soil pLC_{50} values than predicted, the possibility of a nonlinear relationship between efficacy and these properties cannot be ruled out. However, for the set of compounds used in deriving eq 5, attempts to model this possibility by including $C \log^2 P$ or $C \log^2 V_p$ terms did not afford statistically more significant equations.

It is recognized that the model represented by eq 5 assumes that the insecticide does not undergo transformations (chemical or biological) in the soil during the time course of the experiment. Terbufos is recognized to undergo conversion to the corresponding sulfoxide and sulfone in soil. The half-life for the conversion to the sulfoxide ranges from 3.5 to 8 days, and the half-life for the conversion of the sulfoxide to the sulfone ranges from 9 to 11 weeks depending upon the soil type (Chapman et al., 1982). It is reasonable to assume that terbufos could have been converted to the sulfoxide to some degree during the 3-day bioassay. This could well explain why the soil efficacy of terbufos is less than predicted.

Summary. The finding that lipophilicity and volatility significantly affect the soil efficacy of the pyrethroid insecticides has interesting implications in the design of experiments directed at detecting and quantifying field level soil activity. Although the magnitude of these effects could well vary across soil types, the reasonable expectation that they will likely always be important in a soil environment suggests the use of statistically based experimental designs in selecting analogs for field evaluation. The minimum properties which need to be represented in that design would be topical potency, lipophilicity, and volatility.

ACKNOWLEDGMENT

We are grateful to Drs. Richard Phillips, John Engel, and Ernest Plummer, who had originally synthesized some of the compounds cited in this paper, and Mina Reed, Carmela Williams, and Michael Walsh for their technical assistance.

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Received for review January 6, 1992. Accepted May 19, 1992.