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Keywords
Quantitative structure–activity relationship, QSAR, cyanohydrins, fumigation, toxicity, stored-product pest, insecticide, house fly

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QSAR Evaluation of Cyanohydrins' Fumigation Toxicity to House Fly (*Musca domestica*) and Lesser Grain Borer (*Rhyzopertha dominica*)

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Using fumigation toxicity data of 11 natural and synthetic cyanohydrins to house fly (*Musca domestica*) and a stored-product pest, the lesser grain borer (*Rhyzopertha dominica*), the quantitative structure−activity relationships (QSAR) of cyanohydrins were examined by Oxford Molecular CAChe 3.2 and Microsoft Excel. This analysis used eight physicochemical parameters. Correlation between the LC_{50} values for house fly and lesser grain borers was also evaluated. The results showed that log P, polarizability, and molar refractivity are the best descriptors to explain the relationship between the structure of cyanohydrins and biological effects in house flies, and to a lesser degree in lesser grain borers. A significant relationship was also found between the toxicity to house flies and lesser grain borers.

KEYWORDS: Quantitative structure−activity relationship; QSAR; cyanohydrins; fumigation; toxicity; stored-product pest; insecticide; house fly

INTRODUCTION

There are several commercial fumigants on the market today, including methyl bromide, dichlorvos, chloropicrin, and phosphine. However, many of these fumigants have negative ecological or human health effects. Methyl bromide is a known ozone depleter (whose use as a fumigant is being phased out by the U.S. Environmental Protection Agency (EPA)), dichlorvos is a suspected carcinogen, and phosphine has new restrictions on its use. Recent research in this laboratory demonstrated that volatile cyanohydrins that occur naturally in flax and cassava are very potent insect fumigants (*1*). Topical toxicity has been tested with several of the cyanohydrins, but the toxicity values were not as good as those for the fumigation toxicity (*2*). Cyanohydrins' bioactivity is similar to that of several commercial fumigants. Their function in plants is to act as a chemical defense mechanism against herbivores, including insects, and pathogens. These secondary plant metabolites are stored in a stable glucose form until feeding damage occurs; when the glucone is hydrolyzed by activated enzymes, the free cyanohydrin is released and is toxic to insects (*3*−*6*). Nematicidal activity has also been demonstrated for many of the volatile cyanohydrins as part of the current research project. Current research focuses on the development of quantitative structure−activity relationships (QSARs) for prediction of cyanohydrins' insecticidal toxicity.

The descriptors used in the QSARs development were selected to explain one of the major principles of toxicology, which is "the dose makes the poison". This principle states that for a chemical to have adverse effects on an organism, the organism must be exposed to and absorb sufficient amounts of the chemical. Fumigation studies support this principle and show that knowing the volatility of compounds is essential in determining the amount of chemical to which an organism is exposed (*7*). In addition, lipid solubility of chemicals is essential for penetration into the insect cuticle for contact toxicity, although fumigants may enter through spiracles as well. Therefore, volatility and lipid solubility may be critical in determining the toxicity of a compound.

Vapor pressure, which is strongly influenced by intermolecular interactions, is a standard measurement of volatility. These intermolecular interactions can be explained by London dispersive forces, which include dipole−dipole, dipole−induced dipole, and induced dipole−induced dipole interactions. Hydrogen bonding and electrostatic interaction of certain functional groups also play a major role in affecting vapor pressure. Descriptors in the QSAR models were chosen to explain important features of intermolecular interactions. Polarizability, a descriptor used in this study, is a key component in determining the London dispersive forces. Molar refractivity, which is the representation of molar volume and polarizability was also used in these QSAR models. Log P, which represents octanol−water partition coefficient of a chemical, is one of several determinants in the penetration of a chemical into the insect (*8*) and is also an important descriptor in the QSAR models. We also examined molecular weight, molecular connectivity index (0,1,2), shape index (1,2,3), valance connectivity index (0,1,2), highest occupied molecular orbital (HOMO), and lowest unoccupied molecular orbital (LUMO) to explain various components of intermolecular interactions to develop insecticidal QSAR relationships for volatile cyanohydrins.

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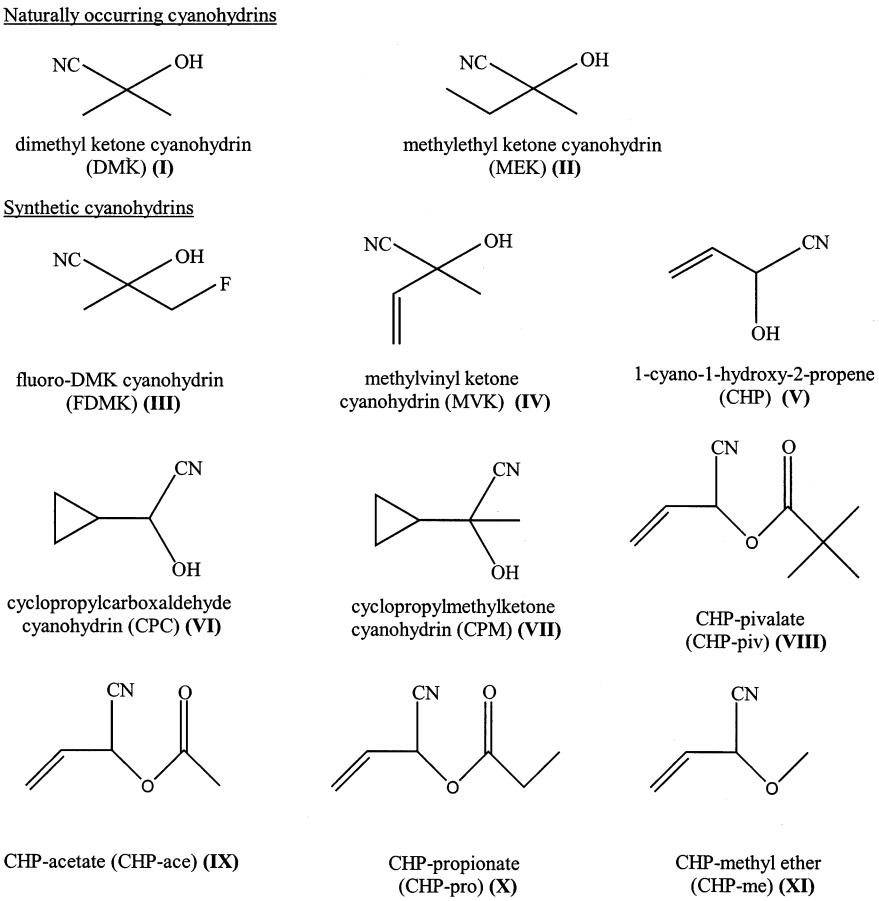

Figure 1. Structures of volatile natural and synthetic cyanohydrins and derivatives tested in insect fumigations.

Table 1. Toxicity and Molecular Descriptors for Eleven Cyanohydrins and Derivatives and Three Commercial Fumigants

	house fly		lesser grain borer				
compound	LC_{50}[a]	95% FL[b]	LC_{50}[a]	95% FL[b]	Log P	polarizability	molar refractivity
I	0.82	0.71, 1.06	4.70	4.11, 5.41	0.354	7.035	22.5
II	0.91	0.71, 1.00	4.14	3.43, 5.14	0.823	8.421	27.1
III	0.87	0.78, 0.97	3.20	2.91, 3.59	0.172	7.040	22.4
IV	2.27	1.96, 2.47	9.47	8.86, 10.50	0.752	8.981	26.9
V	0.67	0.59, 0.76	4.45	1.68, 5.05	0.550	7.796	22.2
VI	1.54	1.44, 1.75	4.12	3.60, 4.63	0.519	8.430	25.0
VII	1.35	1.08, 1.71	3.60	2.97, 4.23	0.722	9.757	29.7
VIII	8.19	6.70, 10.05	14.41	13.10, 16.03	2.534	11.481	45.1
IX	2.08	1.84, 2.40	2.96	2.56, 3.60	0.679	8.356	31.4
X	4.74	4.17, 5.53	5.03	4.60, 5.46	1.307	9.462	36.0
XI	4.22	3.50, 5.05	9.06	7.72, 10.71	0.828	9.330	27.0
chloropicrin	0.49	0.46, 0.60	7.91	7.30, 8.64			
dichlorvos	0.05	0.04, 0.06	1.31	0.95, 1.86			
dichloropropene	8.11	7.39, 10.36	49.29	42.89, 55.60			

[a] LC_{50} value is given in nmol/mL. [b] FL, fiducial limits.

MATERIALS AND METHODS

Chemicals. The structures of natural and synthetic cyanohydrins tested in this study are shown in **Figure 1**. The cyanohydrins were synthesized in the laboratory from the methods of Gassman and Tally (*9*). Purification was achieved by silica gel column chromatography. Cyanohydrin esters were prepared from the cyanohydrins by the methods of Rice et al. (*10*). The chemical structures for all cyanohydrins that were synthesized in this study were confirmed by proton NMR. Commercial fumigants, dichlorvos and chloropicrin, were purchased from Chem Service (West Chester, PA). The active ingredient in Telone, 1,3-dichloropropene, was purchased from TCI America (Portland, OR).

Fumigation Toxicity Testing on Two Species. Insecticidal fumigation toxicity of natural and synthetic cyanohydrins was tested with the house fly and lesser grain borer as described by Peterson et al. (*11*). Adult house flies and borers were placed in a 2.7-L amber jar and a 490-mL glass mason jar, respectively, and a measured quantity of a test compound was applied to filter paper in each jar. The jars were securely capped, and mortalities were recorded after 24 h. The fumigation LC_{50} values were calculated by Proc Probit on SAS (*12*), and the results are presented in **Table 1**. All concentrations were nominal, and results were calculated assuming 100% volatilization of the fumigant from the filter papers in the glass chamber (jar). It is not known if the toxicity is mostly due to the cyanohydrins entering the insects and killing them or HCN from decomposition of the cyanohydrin killing the insect. Vapor pressures were not measured in this study.

QSAR Calculations. Descriptors examined were molecular weight, molecular connectivity index (0,1,2), shape index (1,2,3), valance connectivity index (0,1,2), molar refractivity, polarizability, log P,

Table 2. R^2 (and Cross Validation) of Three Parameters to House Fly and Lesser Grain Borer

parameter	R^2 (and rCV^2) house fly	lesser grain borer
Log P	0.86 (0.79)	0.62 (0.19)
polarizability	0.79 (0.62)	0.53 (0.14)
molar refractivity	0.80 (0.68)	0.40 (0.18)

highest occupied molecular orbital (HOMO), and lowest unoccupied molecular orbital (LUMO). These parameters have been used for explaining the size, shape, and volatility of compounds and for predicting the insecticidal activity. All descriptors and structures were calculated using Oxford Molecular CAChe 3.2 (Beaverton, OR). Regression analysis and cross-validation were calculated using Stat View. The results are shown in **Table 2**. Cyanohydrin structures and energies were obtained by using PM3 calculations.

RESULTS AND DISCUSSION

Fumigation toxicity data and nine parameters were chosen in order to explain cyanohydrin toxicity to house flies. Six of the descriptors evaluated (molecular weight, molecular connectivity index (0,1,2), shape index (1,2,3), valance connectivity index (0,1,2), HOMO, and LUMO) showed a lower correlation with toxicity than did log P, polarizability, and molar refractivity. The R^2 values with molecular connectivity indices (0,1,2) were 0.74, 0.73, 0.47, and for shape indices (1,2,3) were 0.73, 0.53, 0.00, respectively. The R^2 values for valance connectivity indices (0,1,2) were 0.75, 0.56, and 0.32. The R^2 values for HOMO and LUMO were 0.32 and 0.36, respectively. Molecular weight had an R^2 of 0.71. Three of the descriptors examined (log P, polarizability and molar refractivity) showed highly significant correlation between certain structural features of the cyanohydrins and their toxicity to house flies (**Figure 2**). Our results showed that as log P of the cyanohydrins decreased, their toxicity increased. Log P has the highest correlation with toxicity of cyanohydrins of any of the other parameters. Our results also revealed a linear trend of increasing toxicity with decreasing polarizability. A linear correlation was also obtained for molar refractivity (**Figure 2**). This descriptor is related to the potency of London dispersive forces, but it also takes into consideration size and shape of the molecules. Log P, polarizability, and molar refractivity are highly cross-correlated, so the results obtained with those three parameters all describe similar relationships. The high cross-correlation among the three parameters is shown in **Table 3**.

QSARs obtained for lesser grain borer utilized the same three parameters to predict cyanohydrins toxicity as were used for house fly (**Figure 3**). The types of relationships were similar, but the correlations (R^2 values) were not as high. In addition, the relationship between the house fly and lesser grain borer was not highly correlated ($R^2 = 0.68$) as shown in **Figure 4**. **Table 2** shows the comparison of the *R*-squared (fit of the regression) and cross validation (predictive power of the regression) of the three parameters for house fly and lesser grain borer.

The results indicate that log P, polarizability, and molar refractivity values can be used to help predict the toxicity of cyanohydrins in house flies, and to a lesser degree for lesser grain borers. Although a small set of analogues was used to develop these QSAR models, the models will provide insight in designing insecticidally active cyanohydrins. These compounds were selected because they were synthesized to be close analogues of the potent natural cyanohydrins generated in the flax plant. As shown by the R^2 values among the three

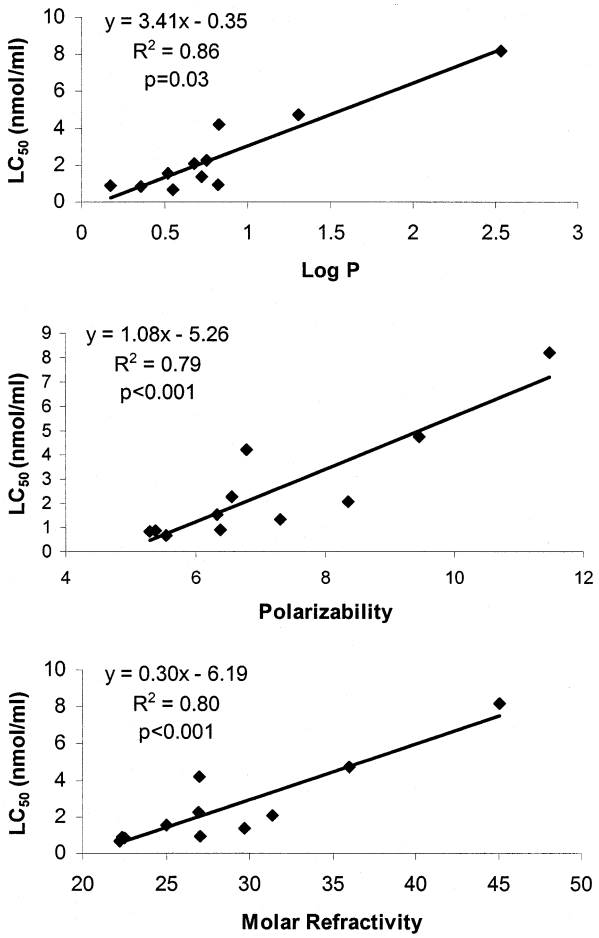

Figure 2. Relationships between three parameters and the toxicity of volatile cyanohydrins to the house fly. For the molar refractivity figure, three data points are superimposed.

Table 3. Cross-Correlation among the Three Parameters

R^2	Log P	polarizability	molar refractivity
Log P	1.0	0.79	0.89
polarizability	0.79	1.0	0.78
molar refractivity	0.89	0.78	1.0

parameters, log P was the best descriptor in predicting toxicity. Polarizability was previously used to calculate the vapor pressures of 479 compounds with good accuracy (*7*). Because polarizability has been previously used to calculate predicted vapor pressures and is used in calculating log P and molar refractivity (*13*), the toxicity correlations for cyanohydrins are probably explained by an increase in exposure of the insects to the chemical, through high volatility. Our assumption is that toxicity of the volatile cyanohydrins is caused by the availability of the cyanohydrin in the vapor phase to enter the insect or its decomposition in vivo to release cyanide ion, or both. Research is in progress to determine if cyanohydrins cause toxicity in the fumigation chamber, or if toxicity stems from spontaneous decomposition of cyanohydrins to hydrogen cyanide in the fumigation chamber.

The QSAR may also explain the reactivities of the various cyanohydrins in the insect body, presumably generating cyanide ion. The fumigation potency of these low-molecular-weight cyanohydrins is probably dependent on (a) their volatility, or (b) their reactivity inside the insect, or both. Research is currently in progress to determine concentrations of the cyanohydrins and HCN in the headspace of the chamber and in

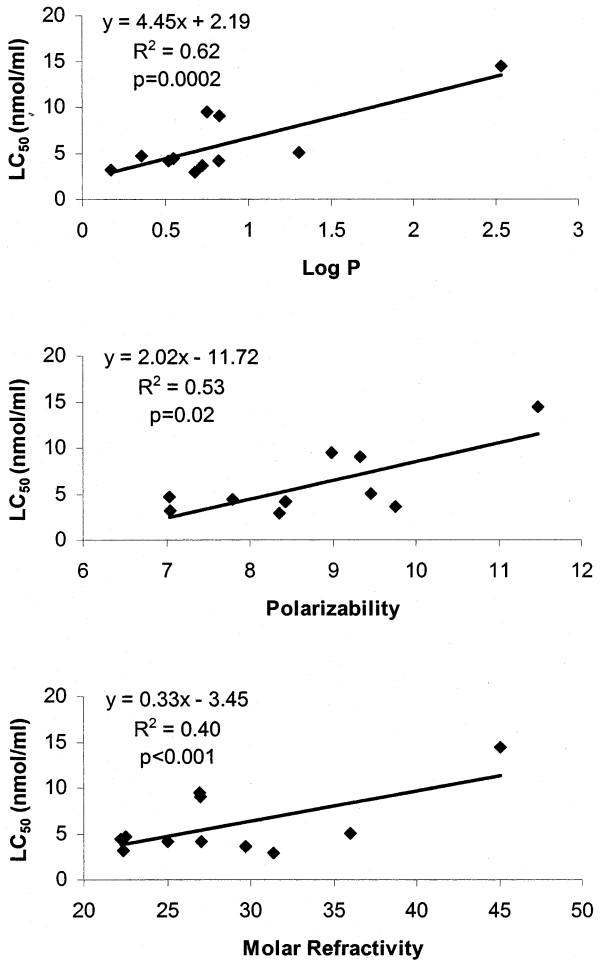

Figure 3. Relationships between three parameters and the toxicity of cyanohydrins to the lesser grain borer. For the polarizability figure, two data points are superimposed.

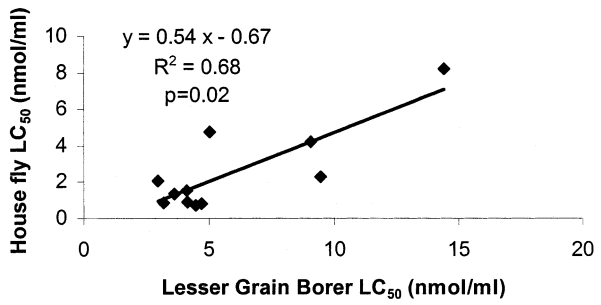

Figure 4. Correlation between the toxicities of volatile cyanohydrins to the house fly and lesser grain borer, using their 24-h fumigation LC_{50} values (nmol/mL).

exposed insects. If the cyanohydrins are decomposing in the chamber to release HCN, then the additional products formed would be volatile carbonyl compounds (acrolein, acetone, fluoroacetone, etc.) which could also contribute to toxicity. If the cyanohydrins are degraded in vivo, the carbonyl compounds may enhance the toxicity to the insect in an additive or synergistic mode.

CONCLUSIONS

The insecticidal potencies of 11 volatile natural and synthetic cyanohydrins against house fly and lesser grain borer are shown in **Table 1**, as well as those of three commercial fumigants. Log P, polarizability, and molar refractivity can be used to predict toxicity of volatile cyanohydrins in house flies. Significant relationships were found between those three parameters and the toxicity to the house fly and lesser grain borer. Some of these cyanohydrins were as potent as current commercial fumigants or more potent. The current research does not allow deduction of the moiety that enters or kills the insects. The more toxic cyanohydrins may be more volatile or may decompose more readily to yield HCN (in the chamber or in the insect). Although the results here do not conclusively explain the underlying principle of the QSAR's, those relationships are still of value in predicting toxicity to the two species of insects.

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