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Modification of Proprietary Chemicals for Increasing Efficacy[1]

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Abstract: Several factors limit the efficacy of nematicides. Consequently, modifications can be made to their active ingredient, formulation, and application to increase their efficacy.
Key words: nematicide, efficacy.

The number of registered nematicides has been greatly reduced over the past decade. Currently, three fumigants and six contact nematicides constitute the bulk of today's $100 million nematicide market (Table 1). Of the nematicides listed, only carbofuran and oxamyl still carry proprietary patents. Thus it could be argued that the necessary modifications have been made to these nematicides.

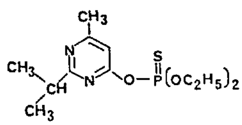
Several factors limit the efficacy of these nematicides, including reaching the target in the soil mass, high cost, inadequate duration of efficacy, and environmental and applicator hazards associated with application. Modifications to overcome these limitations fall into five categories: optimization of active ingredient, formulation, slow release, additives, and application techniques.

Active Ingredient

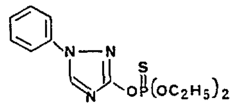
As shown in Table 2, each active ingredient has its own relative level of activity. Many chemicals are composed of isomers, one of which may be more active than the others.

An example of a fumigant made up of two isomers is 1,3-dichloropropene, which is a 50:50 mix of the *cis-* and *trans-* isomers, the *cis-* being considerably more active biologically than the *trans-* isomer. Since the *cis-* form has a boiling point of 104 C and the *trans-* form 112 C, the two enantiomers are separable. The question is this: "Is it economical to undertake such a separation in the production of 1,3-dichloropropene?"

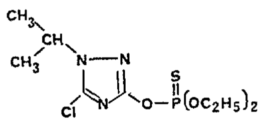
How are chemical leads optimized? One starts with an objective; e.g., look for a plant systemic material which has less mammalian toxicity than aldicarb. One builds upon previous experience. In this case, Ciba-Geigy had previous experience with heterocycle chemistry and expertise with cyanogen chloride, phosgene, isopropylhydrazine as effective elements for heterocycles like 1,2,4-triazoles. Certain insecticidal organophosphates were known to be nematicidal. So we started with diazinon



and triazophos.



Between 1972 and 1979 the 1,2,4-triazole project was researched intensively resulting in 20 patents, with the best commercial product being isazophos (CGA-12223; Miral®).



It is worth noting that in the case of CGA-12223, the corresponding isomer showed no nematicidal activity.

The following four activity factors were considered in the optimization of the general structure:

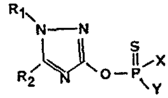


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TABLE 1. Major nematicides currently available in the United States.

Nematicide	Common name
Preplant fumigant	
1,3-Dichloropropene	Telone, Vorlex
Methyl bromide	—
Metham	Vapam
Contact	
Aldicarb	Temik
Carbofuran	Furadan
Ethoprop	Mocap
Fensulfothion	Dasanit
Phenamiphos	Nemacur
Oxamyl	Vydate

(a) systemic in plants, (b) mammalian toxicity, (c) stability in soil, and (d) nematicidal activity.

Initially triazophos analogs were made to evaluate new phenyl derivatives. Results showed that with these new *N*-phenyl derivatives, systemic activity paralleled toxicity; i.e., the more active and more systemic derivatives were very toxic. Because of toxicity the *N*-phenyl derivatives were switched to *N*-alkyl derivatives. Also, when the phosphorus-containing moiety was substituted by a carbamate, the resulting compounds were unacceptably toxic.

Various substitutions were made at R_1, R_2, X, and Y. Results of R_1 substitutions with R_2 = Cl, X and Y = OC_2H_5 are shown in Table 3.

Taking the four activity factors into consideration, the most favorable combination was $R_1 = C_3H_7$, R_2 = Cl, and X and Y each OC_2H_5, which is the structure of Miral.

Another example of active ingredient manipulation can be found in the avermectins (Fig. 1). The avermectins are a complex of chemically related agents produced by the actinomycete *Streptomyces avermitilis.*

TABLE 2. Relative nematicidal efficacy of fumigants (2).

Compound	Number of units of chemical required for direct control
1,2-Dibromo-3-chloropropane	1
1,3-Dichloropropene	8
Chloropicrin	12
Methyl bromide	15
Carbon disulfide	> 100

TABLE 3. Activity of the *R* substitutions.

R_1	Systemicity	Toxicity	Stability	Activity
C_1–C_3	***	**	***	***
≥ C_4	–	**	***	*

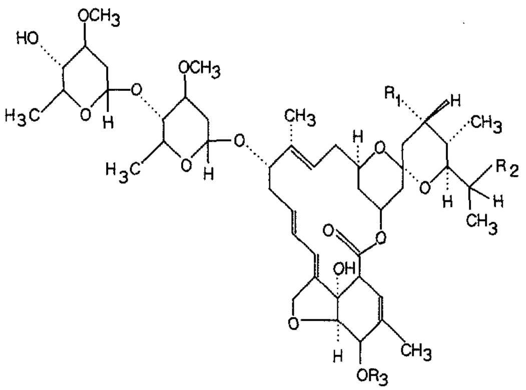
*** Good.
** Medium.
* Unfavorable.
– Nonexistent.

The complex contains four closely related major components—A_1a, A_2a, B_1a, and B_2a—and four minor components—A_1b, A_2b, B_1b, and B_2b each of which is a lower homolog of the corresponding major component. The most active nematicidal avermectin is B_2a (10), having a half-life of 2–5 days in nonsterile soil. In greenhouse experiments, however, nematicidal activity extended for 2 months. Further research showed that the residual efficacy was due to a metabolite, B_2a 23-ketone, derived from microbial transformation of avermectin B_2a. According to this report (10), the ketone metabolite has a soil half-life of about 1 month.

The availability of a toxicant to its target organism is a function of toxicant concentration, time, and distribution. The typical rate of diffusion in soil for a fumigant demonstrates the interrelationships of these three factors (2) (Fig. 2).

Concentration of a soil-applied nematicide means concentration in the soil solution or in the soil atmosphere. Table 4 shows the partitioning and movement of two organophosphates, diazinon and isazophos, in soil compared to two fumigants, ethylene dibromide and 1,3-dichloropropene. Such partitioning in the soil has a great impact on efficacy, as nematodes reside in the soil solution.

Without exception, when applied to soil the major proportion of each of the four compounds becomes associated with the solid phase of the soil. This association can be attributed partially to the fact that the solid particles occupy a larger proportion of the total soil volume than do liquid or gas phases, but this does not diminish the significance of the latter two phases. First,



Avermectin	R_1	R_2	R_3
A_1a		C_2H_5	CH_3
A_1b		CH_3	CH_3
A_2a	OH	C_2H_5	CH_3
A_2b	OH	CH_3	CH_3
B_1a		C_2H_5	H
B_1b		CH_3	H
B_2a	OH	C_2H_5	H
B_2b	OH	CH_3	H

Where R_1 is absent, a double bond (=) is present. Both sugars are α-L-oleandrose.

FIG. 1. Structure of avermectin.

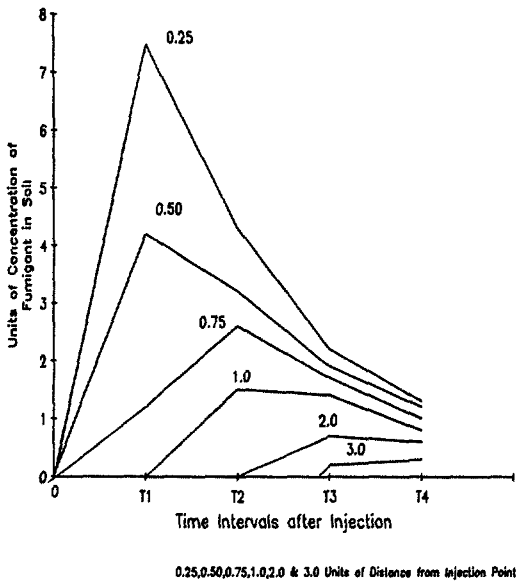


FIG. 2. Relation between concentrations of fumigant in the soil and time interval after injection for various distances from the injection point.

it is generally assumed that pesticides associated with the solid phase of soil are not directly available biologically, although there seems no reason in principle why absorbed pesticides should not be transferred by contact to tissues of nematodes. Second, even with volatile fumigants, less than 1% is found in the soil gas phase. Third, it should be noted that the water–gas partition coefficient for the two organophosphates shows roughly equal diffusion in the vapor and water phases. Yet there is at least a two-fold difference in the chemical half-life of these two products in field soil: 9–17 days for diazinon compared to 42 days for isazophos.

FORMULATION

Nematicides are formulated as fumigants, emulsifiable concentrates (EC), or granulars (G). Table 5 shows typical formulation ingredients in emulsifiable concentrates and granular formulations.

The art of producing a successful pesticide formulation is rapidly becoming a science, but one must realize that a great deal of art persists. Where art exists, many secrets are closely guarded. Consequently, much information is never published. As seen in Table 6, formulation can have a major impact on the efficacy of a compound.

There are few reports on the influence of adjuvants on the behavior of soil-applied pesticides. Surfactants may compete for adsorption sites and thus increase mobility, or they may increase retention by forming micelles around the molecule that are then adsorbed more firmly than the pesticide itself, or they may have no apparent effect.

The hydrophilic surfactant Tween 80 at 1 g/liter was shown to change the octanol: water partition coefficient by one order of magnitude (16). Changes in partitioning can also impact the phytotoxicity and systemic activity of pesticides. Another question is "Does the surfactant influence soil adsorption of the pesticide?" Evidence to

TABLE 4. Proportions of different nematicides in different soil phases.

Compound	Percentage in each phase		
	Air	Liquid	Solid
Ethylene dibromide	0.66	28.4	70.9
Dichloropropene	0.32	6.6	93.1
Diazinon	4.9×10^{-4}	2.8	97.2
Isazophos	1.7×10^{-4}	3.9	96.1

Soil porosity 50%, half-filled with water.

TABLE 5. Typical formulation ingredients.

Ingredient	EC (%)	G (%)
Technical	50	15
Solvent	35	10
Co-solvent	10	—
Emulsifiers	5	—
Granular clay	—	72
Deactivator	—	3

support the positive effects can be seen in the large quantities of surfactants incorporated into the new slow release microemulsion granular pesticide formulations.

SLOW RELEASE FORMULATIONS

Slow release, or controlled release, technology has been widely used in diverse applications such as medicine and baking. Until recently there was limited application of this technology in agriculture.

The relationship between rate of application and the duration of action for a conventional application versus a controlled release formulation, assuming a half-life of 15 days for the pesticide, and a minimum effective dosage of 2.4 g/ha is shown in Figure 3 (6).

Almost all pesticides used to manage organisms in agricultural soils must be applied at excess dosages. Repeat applications are frequently necessary primarily because of decomposition. The advantages of controlled release formulations are 1) reduced mammalian toxicity, 2) extended duration of activity (for equal level of a.i.), 3) reduced evaporative losses, 4) reduced phytotoxicity, 5) active ingredient protected from degradation, 6) reduced environmental impact, 7) controlled release of active ingredient, 8) less active ingredient, and 9) ease of handling.

Why has the pesticide industry not rushed to adopt controlled release technology? Primarily because controlled release preparation and processing are substantially more costly than conventional preparation. However, the starch matrix (starch-xanthate) substrate is relatively inexpensive with starch at a bulk price of 22 cents per kg. The problem lies in the production scale up. Perhaps the starch alkoxide will have better commercial potential for controlled release technology in agriculture.

To date, little work has been done applying controlled release technology to nematicides. The conclusion from greenhouse trials on root-knot with DBCP, diazinon, and ethoprop incorporated into starch xanthate was that size and uniformity of granules are critical to nematicide efficacy (1).

Another type of controlled release is that offered by the carrier Bivert which encapsulates the pesticide in water, facilitating delivery of the pesticide to the desired site of action. Bivert enhanced the activity of isazophos towards *Diabrotica* spp. and *Meloidogyne* spp. in heavy textured soil.

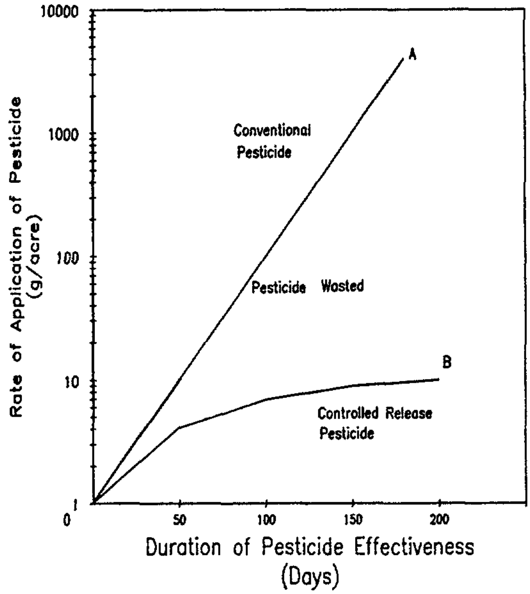


FIG. 3. Relationships between the level of application and duration of action for conventional and controlled release formulation.

TABLE 6. Impact of formulation on the activity of Miral.*

Formulation	Percent galling			
	6 ppm	2 ppm	0.6 ppm	0.2 ppm
Miral technical	0	20	30	100
Miral 4EC	0	30	60	100
Miral 10G	0	0	0	30

* Activity against *Meloidogyne incognita* on cucumbers after 3 weeks in the greenhouse.

ADDITIVES

Development of nematicide synergists has received little attention. Diffusion patterns of methyl bromide in mixture with methyl chloride were studied (15). Admixture of methyl chloride enhanced the activity of methyl bromide compared to the same dosage of methyl bromide alone. Laboratory studies with soil columns demonstrated that more free methyl bromide occurs in the soil gas phase when in combination with methyl chloride, and bromide residues were lower in both the soil and plants, than with methyl bromide alone (15).

The impact of the six synergists, which inhibited either mixed function oxidases or esterases, in combination with aldicarb and phenamiphos was also studied (D. Nordmeyer, pers. comm.). At rates of 10 ppm of the synergists and 1 ppm of the nematicides, no synergism was noted.

Israeli researchers have shown that the efficacy of methyl bromide can be increased substantially by adding *Trichoderma harzianum* to fumigated soil (Y. Elad, pers. comm.). The fungus *Catenaria* sp. was combined with ethoprop, and the mixture provided better control of *Meloidogyne incognita* on tomatoes than ethoprop alone (12). Commercialization of a biocontrol agent may well require concomitant application of a nematicide in order to improve the consistency of its performance. Such combinations may be necessary for efficacy when one considers that an average gram of rhizosphere soil contains 10^9 bacteria, 10^7 actinomycetes, 10^6 fungi, 10^3 protozoa, 10^3 algae, and 1 to 5 nematodes (14). Although the numbers of microbial cells in the rhizosphere are substantial, studies of roots show only 7–15% of the root surface occupied by microbes.

What opportunity is there to use the recently discovered Glycinoeclepin A, a natural hatching stimulus for the soybean cyst nematode, in conjunction with a nematicide? Glycinoeclepin A at 0.0001 ppm was reported to stimulate 80% hatch of *Heterodera glycines* eggs (7). Researchers at Rothamstead have found that many organic compounds stimulate hatch of *H. schachtii* eggs (13). Among the most active hatching stimulants are redox dyes and some quinones. Zinc salts are the only inorganics that enhance egg hatch of all *Heterodera* spp.

Another additive of importance is to the soil rather than to the spray tank. The influence of soil pH on the rate of breakdown (hydrolysis) of pesticides should not be overlooked. Change of soil pH by one unit can alter the breakdown rate of a pesticide from minutes to hours or even days. The impact of lime is also relevant as field studies have led several researchers to conclude that soil structure may be more important than adsorption in controlling movement of solutes in soil (3,4). This concept assumes that soil water can be divided into mobile and immobile fractions and that at least a portion of the mobile water does not come to equilibrium with solutes in the soil.

TABLE 7. Yield from valencia orange trees treated with phenamiphos.

Treatment	Rate (kg a.i./ha)	Fruit yield (mean boxes/tree)* 1976–77	Fruit yield (mean boxes/tree)* 1977–78
Control	—	4.7	4.1
Phenamiphos	11.2	4.6	4.5
Phenamiphos	5.6 ± 5.6	6.5†	5.7‡

* Box = 43.2 kg of fruit.
† $P \leq 0.01$, Dunnett's LSD comparing means against the control.
‡ $P \leq 0.05$, Dunnett's LSD comparing means against the control.

One of the major modes of nematicide decomposition is biodegradation (5). Adaptive changes occur in the soil microbial population so that after an initial lag phase compounds are decomposed rapidly. Such degradation is becoming even more important with the cross-adaptation by microbes to various compounds. Controlling and perhaps even exploiting this inductive process by using microbiological inhibitors provides a fascinating challenge.

APPLICATION TECHNIQUES

One of the primary drawbacks of current nematicides is their short residual activity. One solution to this problem is to make several applications each at a low rate of active ingredient. Two applications of phenamiphos on citrus each at half the normal use rate provided significant yield increases (Table 7) (9). Whereas multiple applications may be feasible with contact nematicides, they are limited with available, registered fumigants on account of phytotoxicity.

The increasing use of drip irrigation has provided an ideal vehicle for making multiple nematicide applications at low rates. Such application is most successful with nematicides having high water solubility. Nematicide performance with in-row crops has been improved by using in-furrow rather than broadcast application.

With the emphasis on improved pesticide placement, research has been conducted using nematicides as seed dressings (11). Thiodicarb applied as a seed dressing has shown promise for early-season nematode control on cotton.

In their publication on control of plant parasitic nematodes (8), the National Academy of Sciences saw the "ideal" nematicide as a systemic chemical that when sprayed on plant shoots is translocated to the roots and kills or repels nematodes feeding on the roots, without imparting harmful residues to the parts of the plant harvested for food or fiber. After many years in industry helping develop new nematicides, I remain optimistic that such an ideal nematicide is feasible.

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