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Naturally Occurring Insecticides

by S. B. Soloway*

Naturally occurring insecticides are abundant and varied in their effects, though but a few are articles of commerce. Even for these, pyrethrum, nicotine, rotenone, hellebore, ryania, and sabadilla, there is a paucity of information on mammalian toxicology and environmental effects. In general, these materials are characterized favorably by low acute toxicity and ready dissipation in nature. Unfavorable aspects of natural insecticides are the contained mixture of active and inactive components and the low active ingredient content on a crop yield basis pointing to a high unit cost. Natural insecticides can serve additionally as leads to unnatural mimics, of which the commercially successful synthetic pyrethroids are prime examples. The chemical nature, relationship of insecticidal activity to chemical structure, occurrence, production, and utilization, registered uses, metabolism, and insect and mammalian toxicity are reviewed.

Introduction

Long before the advent of synthetic insecticides, materials derived from natural sources provided means for controlling pests affecting the human population both directly and indirectly. The utilization of such materials proceeded without attention directed to their toxicological effects. Experience was the discoverer of natural insecticides and also the teacher of how to use them as safely as possible. In all times, the process of empirical discovery has been slow. Contrarily, assessment of the secondary effects of insect control agents is today a relatively rapid, commonplace activity. This activity has expanded in light of the diverse biological effects shown by chemical agents and also their biological transformation products. Multiple biological responses are recognized as well for natural substances of many types. In recognition of such diversity, an understanding of the biological properties of natural insecticides is desirable.

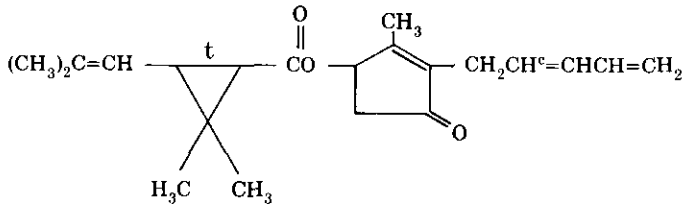
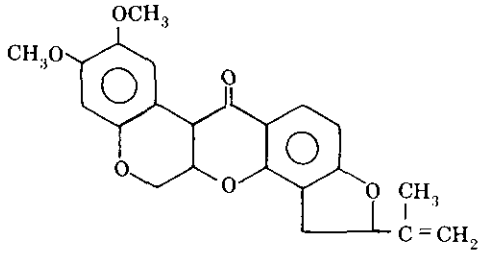
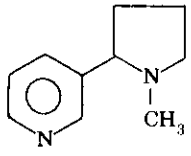
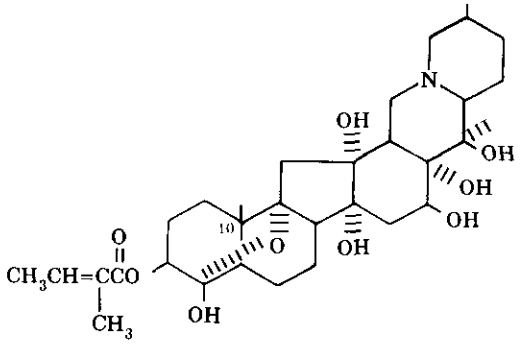
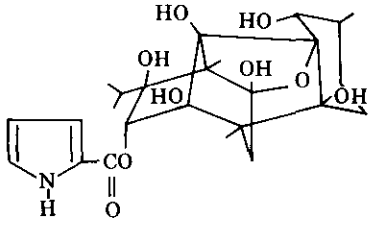
Naturally occurring insecticides are many and varied and descriptions of them abound in books and reviews. The human health aspects of these materials are known only in a few instances, and therefore a complete rendition of the nature and known properties of all natural insecticides would be superfluous. In light of information available and time allowed, the present discussion is restricted to naturally occurring insecticides that are articles of commerce and derived from plant sources. The 1975 *Farm Chemicals Handbook,* lists under insecticides the following plant materials (*1*): nicotine alkaloid; nicotine sulfate; rotenone (cube); rotenone (derris); hellebore; ryania; sabadilla; and pyrethrum. These plant-derived materials constitute the subject of this paper. The compilations by Jacobson and Crosby (*2*) and Metcalf (*3*) are the main sources of the information here presented.

Chemical Nature

The chemical constitution of commercial natural insecticides is of two types: one characterized by the presence of only C, H, and O (pyrethrum and rotenone); the other by the presence of nitrogen (nicotine, hellebore, sabadilla, and ryania). As illustrated in Table 1, the active principles of these materials generally have complex structures. Although the chart depicts but one specific structure for each material, that for the most active or predominant principle, natural insecticides contain a number of active components. Obviously, total extracts contain numerous, inactive substances as well.

*Shell Development Company, Modesto, California 95352.

Table 1. Chemical nature of natural insecticides.

Name	Structure
Pyrethrin I	
Rotenone	
Nicotine (*Nicotiana* sp.)	
Cevadine (*Veratrum sabadilla*)	
Ryanodine (*Ryania speciosa*)	

Relationship of Insecticidal Activity to Chemical Structure

Pyrethrins

Table 2 shows the relative toxicity of pyrethrum principles to *Musca domestica*. Not unexpectedly, variations in the substitutents in both the acid and alcohol parts produce significant effects on activity, as well as knockdown. The pentadienyl side chain in pyrethrin I and II imparts slightly greater toxicity than the butenyl counterpart in cinerin I and II, or pentenyl in jasmolin I and II. A greater difference is shown between the dimethylvinyl group and (methoxycarbonyl) methylvinyl in the acid components of pyrethrin II and cinerin II, respectively, the former being appreciably more active. Of even greater significance is the effect of optical isomerism on activity. The natural *d*-acid in combination with either the natural *d*-alcohol or the *l*-alcohol gives esters that are five to ten times more active than the *l*-acid esters. The geometrical isomerism of the acid component has a lesser effect, the natural *trans* form being about twice as active as the *cis*.

Rotenone and Related Materials

Information on structure-activity relationships is summarized in Table 3. Rotenone, which is present up to 40% in derris resins, is more active than the other principal components, dequelin and toxicarol. The last two differ from the first in having a pyran E-ring in place of dihydrofuran bearing an unsaturated side chain. In addition, toxicarol is substituted nuclearly (D-ring) by a hydroxyl group, which is likely the cause of its virtual inactivity.

Table 2. Toxicity of pyrethrins and cinerins to *Musca domestica*.

Constituent	Relative toxicity (pyrethrins = 1.0)
Pyrethrin I	2.00
Pyrethrin II	0.46
Cinerin I	1.38
d-cis-cineronyl *d-trans*-chrysanthemate	0.67
l-cis-cineronyl *d-trans*-chrysanthemate	1.22
d-cis-cineronyl *l-trans*-chrysanthemate	0.17
l-cis-cineronyl *l-trans*-chrysanthemate	0.12
Cinerin II	0.35

Table 3. Toxicities of rotenone and related materials.

Compound	LD_{50} as stomach poison to fourth instar *B. Mori*, mg/kg	LC_{50} to house fly (in acetone, in 72 hr), mg/ml	Relative lethal concentration as suspensions to *A. rumicis*, %
Rotenone	3	0.30	0.0005
Dihydrorotenone	10		
1-Dihydro-rotenone	—	0.43	
1-β-Dihydro-rotenone	—	0.71	
Dehydrorotenone	>400		
Deguelin	10-12	2.80	0.005
Tephrosin	30-60	—	0.02
Toxicarol	>1540	—	0.2
Rotenol	>510		
1-α-Toxicarol	—	—	—
Sumatrol	—	—	—
1-Ellipton	—	—	—

Table 4. Toxicity of nicotine and related materials.

Compound	Relative LC_{50} *A. rumicis*
l-β-Nicotine	1
d-β-Nicotine	5
l-β-Nornicotine	0.5
d-β-Nornicotine	0.7
dl-β-Nornicotine	1
dl-α-Nornicotine	31
dl-β-Nicotine	2
dl-α-Nicotine	31
l-β-Anabasine	0.1
Nicotyrine	13

Table 5. Occurrence and utilization of natural insecticides.

	Plant sources	Content, %	Production, lb/acre	Utilization, M lb, 1972
Pyrethrins	*Chrysanthemum cinerariae folium*, flower	0.9–1.3	10	250
Rotenone	*Derris elliptica*, root	5–9	—	150
	Lonchocarpus utilis, root	8–11	—	
Nicotine	*Nicotiana tabacum*, leaf	2–5	100	180
	Nicotiana rustica	5–14		
Sabadilla	*Veratrum sabadilla*, seed	0.3 (alkaloids)	—	—
Hellebore	*Veratrum alba*	—	—	—
Ryania	*Ryania sp.*, stem	0.2 (ryanodine)	—	—

Nicotine and Related Materials

Table 4 shows the relative toxicity of nicotine and its natural congeners to *Aphis rumicis*. Immediately recognizable is the effect of optical isomerism. The natural *l*-isomers are appreciably more toxic than the *d*-isomers. Of equal or greater significance is the effect of having a hydrogen in place of methyl joined to nitrogen of the saturated heterocycle; the N-H compounds are more active. This difference is particularly striking when the saturated heterocycle is the six-membered piperidine; anabasine is ten times as active as nicotine. Conversely, when the aromatic pyrrole ring is joined to pyridine, as in nicotyrine, the activity is one-tenth that of nicotine.

The relative simplicity of the nicotine structure and its marked neurophysiological properties have invited the synthesis and testing of many analogs. None appears to approach the practical activity and usefulness of nicotine.

Sabadilla, Hellebore, and Ryania

Information on the insecticidal activity of the pure components of these materials is scanty. Cevadine is less toxic to houseflies than veratridine, its corresponding 3,4-dimethoxybenzoate, though both are more active than pyrethrins. Conversely, cevadine is more effective than veratridine against the large milkweed bug (*Oncopeltus fasciatus*) and the red-legged grasshopper (*Melanopas femur-rubrum*). Whereas changes in the esterifying acid, as between the sabadilla components cevadine and veratridine, are expected to impart differences in activity, greater significance is likely to reside in the effects produced by modifications of the polynuclear alcohol of these veratrum alkaloids. Unfortunately, data for such modifications are not in hand. Ryania components suffer similarly.

Occurrence, Production, and Utilization

Table 5 presents the main plant sources of the natural insecticides under discussion and the content of their principal components. Pyrethrins occur in the flower parts of their parent to about 1% whereas the total alkaloid content of sabadilla seeds and ryania stems is but a few tenths of a percent. Contrarily, rotenone and nicotine are present in their plant sources to an appreciable extent, 5–11% for the former in roots and 2–11% for the latter in tobacco leaf. Of related interest is that sugar cane contains about 10% of sucrose. Recognition should be given, however, to the amount of

Table 6. Registered uses of pyrethrins[a]

Use[b]	No. of uses	Tolerance	Dosage, lb/acre
A Bush and vine fruits	13	Exempt	0.5 (dust) 0.05 (spray)
B Deciduous fruits and nuts	22	Exempt	0.5 (dust) 0.05(spray)
C Forage crops	7	Exempt	0.3 (dust) 10.0 g/a (spray)
D Grain	9	1-3 ppm (with 8-20 ppm of piperonyl butoxide)	0.6 lb/1000 bu (dust) 90 g/1000 bu (spray)
E Vegetables	49	Exempt	20 g/a (spray) 0.3 lb/a (dust)
F Animals	6	0.5 (in milk fat) 0.1(in meat)	0.1-1.12% (in oil)
G Miscellaneous	8	1 ppm (with 8 ppm piperonyl butoxide)	Various
H Agricultural premises		As in F	Various

[a]As of May 31, 1969.
[b]Limitations: none for A,B,C,E; various for D,F,G,H.

Table 7. Registered uses of rotenone[a,b]

Use	No. of uses	Tolerance	Dosage, lb/acre	Limitations
A Bush and vine fruits	13	Exempt	0.75	1 day
B Citrus	7	Exempt	2	1 day
C Deciduous fruits	14	Exempt	1	1 day
D Forage crops	7	Exempt	0.75	1 day
E Vegetables	48	Exempt	0.25-1.75	1 day generally

[a]As of May 31, 1969.
[b]Plus related derris and cube resins and extractives.

Table 8. Registered uses of nicotine.

Use	No. of uses	Tolerance	Dosage, lb/acre	Limitations
A Vegetables[a]	5	2 ppm	1-2 tsp. 40% alkaloid/gal water	Various
B Flowering plants[a]		—	1 lb 0.5% / 50 ft[a]	Various
C Deciduous fruits[b]	5	2 ppm	3 tsp 40% solution/gal water	Foliage application
D Citrus[b]	4	2 ppm	3 tsp 40% solution/gal water	Foliage application
E Vegetables[b]	18	2 ppm	3 tsp 40% solution/gal water	Foliage application
F Melons[b]	8	2 ppm	3 tsp 40% solution/gal water	Foliage application
G Ornamentals		—	3 tsp 40% solution/gal water	Foliage application
H Poultry[c]		1 ppm in eggs, meat, fat and meat by-products of poultry	2 drops 40% solution/bid	Various

[a]As of August 30, 1973.
[b]As of November 14, 1972.
[c]As of May 30, 1975.

Table 9. Registered uses of sabadilla[a]

Use	No. of uses	Tolerance	Dosage, lb/acre	Limitations
A Bush and vine fruits	13	Exempt	12.0[b]	No time limitation
B Citrus	7	Exempt	0.2[c]	No time limitation
C Deciduous fruits	14	Exempt	12.0[b]	No time limitation
D Forage crops	7	Exempt	10.0[b]	No time limitation
E Vegetables	46	Exempt	10.0[b]	No time limitation

[a]As of May 31, 1969.
[b]Whole ground seed.
[c]Alkaloids.

sugar cane produced per acre, which is about 90 tons in Hawaii and 25 tons in Louisiana (*4*). The contrast between sugar production, on one hand, and pyrethrin and nicotine, on the other, is remarkable, the yields of the last two being about 10 and 100 lb/acre, respectively, and of the first, 5,000-18,000 lb/acre.

The data on utilization are import figures reported by the United States Department of Agriculture (*5*).

Registered Uses

Tables 6–10 summarize the main uses registered by EPA for the natural insecticides under discussion. In general, these insecticides are permitted for use on many crops, and in some instances on animals. Noteworthy are the established tolerances. Rotenone, sabadilla, and ryania are totally exempt from any tolerance. Pyrethrins are generally exempt except for grain and animal use, whereas nicotine has tolerances for all registered food crops.

Metabolism

The major metabolites of rotenone and nicotine, respectively (*5*), are shown in schemes (1) and (2). The four metabolites of rotenone arose directly, and not from any other intermediate, from treated microsomal fractions of housefly abdomens, mouse and rat livers. The metabolic pathway shown for nicotine is the primary process occurring in plants, insects, and mammals, including man. In each case, cotinine is the principal metabolite.

Inspection of the depicted transformations reveals common processes, all oxidative in nature. Oxygen insertion occurs between carbon and hydrogen where this linkage is allylic, benzylic, or α to an electron-withdrawing group such as carbonyl or amino. Another process involves the formation of a diol from an olefin, presumably by initial formation of an epoxide, or mechanistic equivalent, and subsequent hydration.

These oxidative processes are essentially universal as to both substrates and biological systems. The pyrethrins undergo similar metabolic transformations, and in addition are prone to cleavage of the ester group. Information on metabolism of the sabadilla and ryania alkaloids does not appear to be available.

Insect and Mammalian Toxicity

LD_{50} values for typical insects and mammals are presented in Tables 11–15. A comparison of the acute values indicates, in general, that the toxicity of the natural insecticides to insects, administered under use conditions, is greater than to mammals, administered orally. This distinction probably reflects differences in penetration and metabolism. These factors may also account for the greater acute as well as chronic toxicity of rotenone relative to pyrethrins. Besides the oxidative pathways recognized for these materials, the pyrethrins are cleaved by esterases, a process that operates freely in mammalian systems. Although acutely toxic to mammals, spray residues of nicotine are not a hazard from the standpoint of chronic toxicity owing to its volatile nature.

Noteworthy is the acute oral toxicity to mice of the primary rotenone metabolites. Rotenolone I

Table 10. Registered Uses of ryania.[a,b]

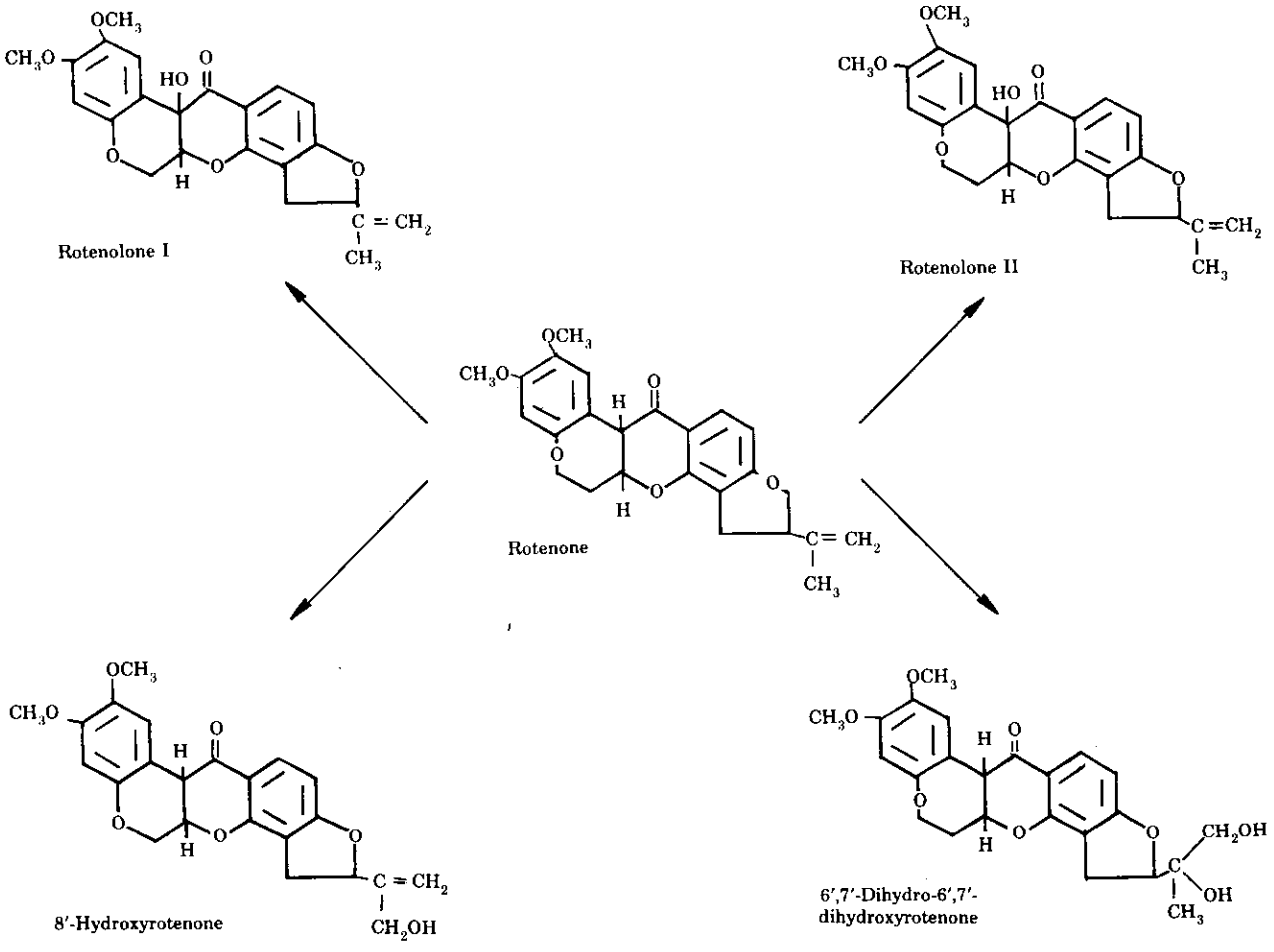
Use	Tolerance	Dosage (actual), lb/acre	Limitations
Apples	Exempt	72.0	No time limitations
Citrus	Exempt	0.8[c]	Apply as a sugar bait; no time limitations
Corn	Exempt	20.0	No time limitations
Cranberries	Exempt	25.0	No time limitations
Pears	Exempt	72.0	No time limitations
Quinces	Exempt	72.0	No time limitations
Sugar cane	Exempt	8.0	No time limitations

[a]Ryania alkaloids from powdered stems of *Ryania speciosa*..
[b]As of May 31, 1969.
[c]Pure ryanodine.

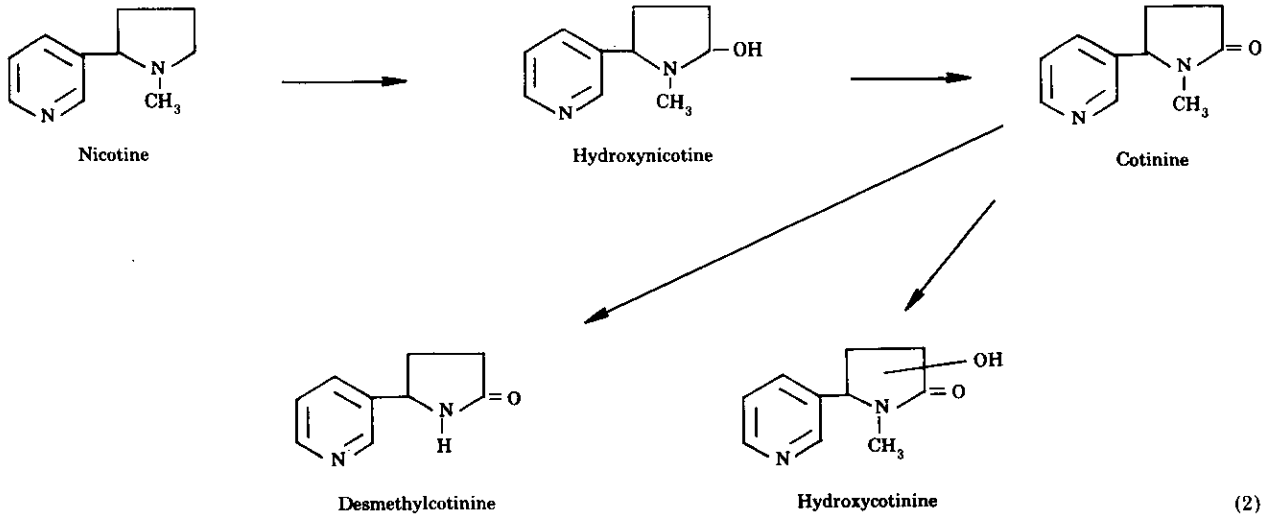
Table 11. Toxicity of pyrethrins.

Organism	Acute toxicity LD_{50}, mg/kg	Chronic toxicity (2 yr), ppm	Primary action
Aedes aegypti (spray)	0.5	—	CNS block (insects)
Musca domestica (spray)	31	—	
Oncopeltus fasciatus (topical)	8	—	
Rat (oral)	1500	1000; no tissue damage	
Rabbit (dermal)	300	5000[a]	
Dog (IV)	7	—	

[a]Effects in one study, not another.


Rotenolone I
Rotenolone II
Rotenone
8′-Hydroxyrotenone
6′,7′-Dihydro-6′,7′-dihydroxyrotenone

(1)


Nicotine
Hydroxynicotine
Cotinine
Desmethylcotinine
Hydroxycotinine

(2)

Table 12. Toxicity of rotenone.

Organism	Acute toxicity LD_{50}, mg/kg	Chronic toxicity (2 yr), ppm	Primary action
Bombix mori larva (oral)	3	—	Block of mitochondrial $NADH_2$ dehydrogenase
Oncopeltus fasciatus (topical)	60	—	
Periplaneta americana (injected)	7	—	
Periplaneta americana (topical)	>2000	—	
Rat (oral)	132	2, no damage 5, tissue damage	
Rat (IV)	6	—	
Rabbit (dermal)	> 940	—	
Mice, male (oral)			
Rotenone	2.8	—	
Rotenolone I	4.1	—	
Rotenolone II	> 25	—	
Hydroxyrotenone	2.6	—	
Dihydrodihydroxyrotenone	10	—	

Table 13. Toxicity of nicotine.[a]

Organism	Acute toxicity LD_{50}, mg/kg	Chronic toxicity (43 weeks), ppm	Primary action
Bombix mori larva (oral)	10	—	Central nerve ganglia: excitation (low concentration) and paralysis (high concentration)
Bombix mori larva (topical)	4	—	
Apis mellifera (topical)	315	—	
Oncopeltus fasciatus (topical)	315	—	
Rat (oral)	55	60	
Rat (IV)	7	—	
Rabbit (dermal)	50	—	

[a]Nornicotine and anabasine show similar mammalian toxicity.

Table 14. Toxicity of sabadilla.

Organism	Acute toxicity LD_{50}, mg/kg	Primary action	Teratogenicity
Periplaneta americana (bait)	300	Acts on nerve fibers, skeletal muscle, and cardiovascular system	Observed in sheep for alkaloids of *Veratrum califorcum*
Rat (oral) ground seeds	4000		
Rat (dermal)	no toxicity		
Mouse (IP), cevadine	3.5		
Mouse (IP), veratridine	1.35		
Mouse (IV) veratridine	0.42		

Table 15. Toxicity of ryanodine.

Organism	Acute toxicity LD_{50}, mg/kg	Primary action
Oncopeltus fasciatus (topical)	25	Direct and irreversible contractile action on vertebrate and invertebrate muscle
Rat (oral)	750	
Rat (IP)	0.32	
Dog (oral)	150	
Dog (IV)	0.075	

and hydroxyrotenone are as toxic as rotenone, whereas rotenolone II and dihydroxyrotenone are significantly less so.

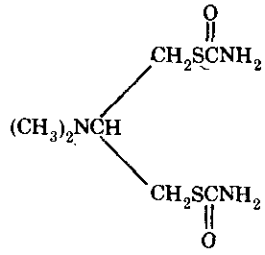
Conclusion

The information presented here allows a number of generalizations with respect to the use of naturally occurring insecticides. Advantages of natural insecticides are the low mammalian toxicity, oral and dermal, for complex molecules and the ease with which they are metabolized; disadvantages are that they are mixtures of active and inactive components and their low content of active ingredient(s) on a crop yield basis.

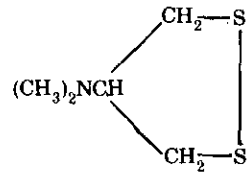
Favorable to the use of natural insecticides is their generally low acute toxicity to mammals and ready dissipation. Being products of biosyntheses, the natural toxicants have functional groups and conformations with which metabolizing enzymes may interact. Their ready metabolism is then a sequential act of nature.

Unfavorable aspects of natural insecticides are the contained mixture of active and inactive components and the low active ingredient content on a crop yield basis. The latter characteristic points to a high unit cost. Obviously, should a natural insecticide be cultivatable much as sugar, a broadly usable product would result. The disadvantage of natural insecticides being mixtures would stem from the complexity of determining the properties, residual and toxicological, of more than one component.

Aside from the advantages mentioned above, natural insecticides can serve as leads to unnatural mimics, of which synthetic pyrethroids are prime examples. Although synthetic rotenoids, nicotinoids, and mimics of other natural insecticidal substances have not shared similar success, the potential for discovery exists. Besides the successful pyrethroids, another, albeit minor, example exists in the form of cartap, which is essentially a derivative of nereistoxin, a naturally occurring insecticidal substance isolated from marine segmented worms, *Lumbrineris heteropoda* and *L. breviccirra* (7). Toxicity data for these substances



Cartap



Nereistoxin

are given in Table 16. Cartap is used against rice insects, among others, but does not appear to be EPA registered.

Table 16. Toxicity of cartap and nereistoxin

Organism	LD_{50}, mg/kg Cartap	LD_{50}, mg/kg Nereistoxin	Primary action
Rice stem borer larva	1.5	4.0	Blocks cholinergic impulses
Rat (oral)	225	—	

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