terone in stimulating reptilian oxidative metabolism. This is interesting since oestrogen has many important biological actions opposite to those of testosterone.

There are only a few reports on the effects of oestrogens on oxidative metabolism of lower vertebrates. Hoar[8] injected goldfish with stilbesterol and observed a marked stimulation of oxidative metabolism. He offered the suggestion that the steroid may increase in some way the reactivity of neuromuscular mechanisms thus promoting locomotor activity which indirectly results in an increased demand for oxygen. But this possibility has not been explored further. It is possible that the action of oestrogen on reptilian oxidative metabolism may be brought about in several ways viz, by stimulating metabolic pathways thereby increasing the substrate concentration or by acting on the respiratory chain.

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Avermectins: novel insecticides, acaricides and nematicides from a soil microorganism

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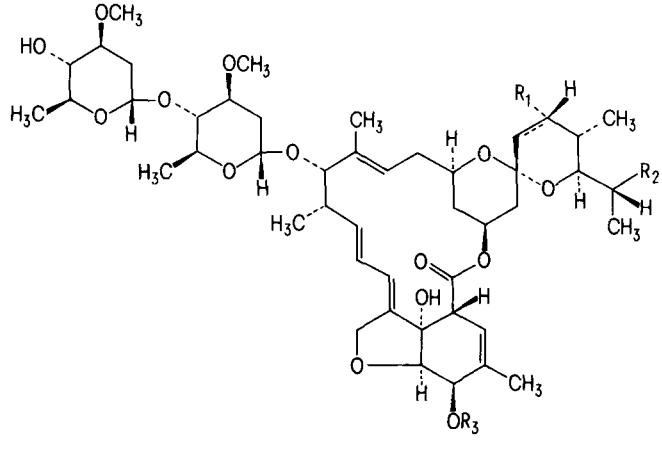
Summary. The avermectins, streptomycete-derived macrocyclic lactones originally isolated as antiparasitic agents, have also demonstrated high potencies in laboratory evaluations against insect pests in several orders, phytophagous mites and the plant-parasitic nematode, *Meloidogyne*. Studies suggest that the avermectins' mechanism of toxicity is fundamentally different from those associated with current natural and synthetic pesticides.

We report here the broad spectrum agricultural pesticidal activity of the avermectins, a new class of macrocyclic lactones isolated from the soil organism *Streptomyces avermitilis*[3]. These compounds were originally discovered in the MSDRL screening programs as anthelmintic agents, demonstrating potencies in the 10-300 parts per billion range (μg/kg b.wt) when administered to sheep, cattle, dogs and poultry infected with a spectrum of common gastrointestinal parasites[4]. Initial indications of insecticidal activity were shown in tests against the confused flour beetle[5] and the ectoparasitic larvae of the sheep blowfly[6]. Subsequent work has also demonstrated potent activity against other veterinary ectoparasites including mites and ticks[7]. In recent laboratory and field evaluations, we have extended these observations to include agricultural and household insect pests of several orders, phytophagous mites and the plant-parasitic nematode, *Meloidogyne incognita*.

The structures of the 8 major components (designated A_{1a}, A_{1b}, B_{1a}, B_{1b}, A_{2a}, A_{2b}, B_{2a}, B_{2b}) of the avermectin complex are represented below[8]. Of these, avermectins B_{1a} and B_{2a} are the most promising candidates as agricultural pesticides.

In laboratory studies, avermectin B_{1a} has demonstrated high toxicity for the 2-spotted spider mite *(Tetranychus urticae)* on bean plants compared to commercially used acaricides. When applied in solution directly onto adult and nymphal populations on foliage, avermectin B_{1a} was 50-200 times as potent as these materials, with an LD_{90} of 0.02-0.03 ppm (table). Avermectin B_{1a} has also shown high activity against several other tetranychid and eriophyid mites, including the citrus rust mite *(Phyllocoptruta oleivora)*, citrus red mite *(Panonychus citri)* and the strawberry spider mite *(Tetranychus turkestani)*.



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, the double bond (=) is present. Both sugars are α-L-oleandrose.

In studies in which bean leaves were dipped into avermectin B_{1a} solutions at 0.5-1.0 ppm and challenged with a mixed adult and nymph mite population 7-14 days later, excellent persistance was observed and foliar residues were found to be lethal to the 2-spotted spider mite populations for periods up to 1 month. Avermectin B_{1a} has shown activity against all motile mite stages (adults, nymphs and larvae); however, no direct ovicidal action has been observed at doses up to 25 ppm. Laboratory evaluations suggest that avermectin B_{1a} kills the 2-spotted spider mite both by contact and ingestion action. This natural product has a slow-acting effect in mites at the LD_{90} dose level. Although mites become moribund soon after contact with avermectin B_{1a}, they die over a 3-4 day period. Field observations have indicated that avermectin B_{1a} is not rapidly degraded by sunlight and displays excellent rainfall tenacity once the pesticide residue has been allowed to dry on the foliage and fruit.

The avermectin family of compounds and avermectin B_{1a} in particular, has shown excellent activity in the control of several pests in the order Lepidoptera, Coleoptera, Homoptera, Orthoptera, Diptera, Isoptera and Hymenoptera. The table gives LD_{90}'s values for avermectin B_{1a} for the control of larval forms of several of these insects in foliar residue assays.

As mentioned previously for mites, avermectin B_{1a} also displays a slow toxic action in insects, relative to conventional organophosphate and pyrethroid insecticides. Insects in contact with foliar residues of B_{1a} die approximately 4 days after initial exposure. We have noted that in lepidopterous larvae, exposure to avermectin B_{1a} rapidly produces a paralysis in the pseudopodia (hind legs) that interferes with the insects' ability to move about and feed on the foliage. As a result of this action, feeding inhibition has been observed at dose levels considerably lower than those which produce direct insect mortality. In a bait formulation used against the red imported fire ant *(Solenopsis invicta)*, avermectin B_{1a} halted egg production in the queen at levels (about 0.12 g per hectare) that are not 100% lethal to the worker ants. This condition appears to be permanent in the queen and thus of potential utility for fire ant control[9]. Larval flies and mosquitoes exposed to avermectin B_{1a} in their rearing medium AT 2-50 ng/ml (depending on the species) fail to pupate. Adult survivors of sublethal doses are apparently fertile[10].

Whereas avermectin B_{1a} has shown optimum efficacy against mites and insects, avermectin B_{2a} is the more potent against the rootknot nematode, *Meloidogyne incognita,* in greenhouse tests. When incorporated into soil, avermectin B_{2a} exhibits excellent control of this nematode in the range of 0.16 to 0.24 kg/ha and is about 10-30 times as potent as several commercial contact nematicides.

Avermectin B_{2a} has a half-life of 2-5 days in non-sterile soil, depending on soil moisture and temperature; however, in greenhouse experiments using sandy-loam soil, nematicidal efficacy and plant protection were shown to extend for as long as 2 months. Subsequent investigation showed that this residual action was due to a nematicidally active metabolite, derived from the microbial transformation of avermectin B_{2a}, having a soil half-life of about 1 month[11]. The nematicidal efficacy of avermectin B_{2a} is sensitive to soil type and has been shown to be least effective in soil of high organic content (> 10%). At dosage levels as high as 10 kg of avermectin B_{2a} per hectare, it was non-phytotoxic to tomatoes and cucumbers in the greenhouse.

Previous studies on the mode of action indicate that avermectin B_{1a} is a γ-aminobutyric acid (GABA) agonist that eliminates the GABA-mediated inhibitory postsynaptic potentials as well as the excitatory postsynaptic potentials at the lobster neuromuscular junction[12]. It is thus likely that the avermectins act by inhibiting nervous signal transmission at the neuromuscular junctions of arthropods. In nematodes, avermectin B_{1a} blocks signal transmission from the ventral interneurons to excitatory motoneurons[13]. It has no effect on cholinergic nervous systems and is essentially non-toxic for cestodes and trematodes, organisms lacking the GABA system.

In conclusion, the avermectin natural products are pesticides possessing novel chemistry and mode of toxic action that have exhibited high potencies for a broad spectrum of invertebrate pests.

Efficacy of foliar residues of avermectin B_{1a} against adult mites and larval insects

Insect	LD_{90} (ppm)*
Two-spotted spider mite *(Tetranychus urticae)*	0.02-0.03
Tomato hornworm *(Manduca sexta)*	0.02
Colorado potato beetle *(Leptinotarsa decemlineata)*	0.03
Mexican bean beetle *(Epilachna varivestis)*	0.20
Cabbage looper *(Trichoplusia ni)*	0.75-1.2
Southern armyworm *(Spodoptera eridania)*	6.0
Corn earworm *(Heliothis zea)*	1.5
Pea aphid *(Acyrthosiphon pisum)***	0.4

*These values are based on mortality observations taken 72 to 96 h after the larvae were place on foliage. **Adults were used in this test.

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