Related References:
Shoop, WL, Mrozik, H, Fisher, M.
Structure and activity of avermectins and milbemycins in animal health

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Ivermectin/ Doramectin/Moxidectin - Structure and Generation

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A Scientific Review

Summary
Milbemycins, first described in 1974, and avermectins, first described in 1979, are macrocyclic lactones produced by fermentation of Streptomyces species. Moxidectin is derived from chemical modification of nemadectin, a fermentation product of Streptomyces cyanogriseus noncyanogenus. Ivermectin is a semi-synthetic derivative of the natural avermectins, including abamectin, produced during fermentation of Streptomyces avermitilis. Mutation of S. avermitilis by chemical modification results in production of doramectin, structurally closer to abamectin than ivermectin. Although there are no differences between avermectins and milbemycins in mode of action, the structural variation between the different members of the macrocyclic lactones account for inherent differences, including solubility, efficacy and safety. The principle that successive "generations" of products are associated with improvements in efficacy and potency, as they are with the benzimidazoles does not apply to the macrocyclic lactone endectocides.

Milbemycins
Milbemycins include milbemycin oxime, produced by fermentation of the actinomycete Streptomyces hygroscopicus aureolacrinosus, and moxidectin, produced chemical modification of nemadectin, a product of fermentation of Streptomyces cyanogriseus noncyanogenus. Milbemycins and avermectins are macrocyclic lactones characterized by the presence of a 16-membered lactone ring. The difference between milbemycins and avermectins is a disaccharide substituent at carbon 13, present in the avermectins and absent in the milbemycins. Although the acaricidal properties of the milbemycins were initially recognized, their anthelmintic activity was only identified subsequent to discovery of the avermectins.(1)

Avermectins
Avermectins available in the United States for use in animal health are ivermectin and doramectin. All are products of fermentation of Streptomyces avermitilis. During fermentation, the actinomycete produces four homologous pairs of closely related macrocyclic lactones. These pairs are further subdivided into the major components, A1a, A2a, B1a and B2a.
and minor components A1b, A2b, B1b and B2b.

Avermectin B1a serves as the basis for the semi-synthetic 22,23-dihydro analog which comprises at least 90% of the active component of commercial ivermectin. The other avermectin component of ivermectin is the B1b homolog, at a level of no more than 10%.

Doramectin was produced in the Pfizer laboratories as a result of induced mutation of *S. avermitilis.*(2) After mutation, the actinomycete produced a range of avermectins, one of which was doramectin. The only structural difference between abamectin and doramectin is the different substituent at the R25 position; both compounds differ from ivermectin in the dihydro modification at the 22,23 position. Doramectin is therefore structurally closer to abamectin than it is to ivermectin.

**Potency of Compounds**

![Potency Graph](image)

**Generation**

The concept of "generation" is associated with the benzimidazoles, and is reflected in chronological appearance, in efficacy claims and in reducing dose rate, a result of higher potency of later compounds. For instance, thiabendazole was first released in the early 1960s for use in cattle to control nematodes at a dose rate of 66 to 110 mg/kg. In the early 1980s oxendazole was released for use at 4.5 mg/kg, with claims for efficacy against tapeworms and nematodes, including *Dictyocaulus viviparus* and inhibited larvae *Ostertagia ostertagi.*

The generation concept does not apply to the macrocyclic lactone endectocides. All have efficacy against the same parasites, although there may be variations in potency, safety profile and metabolism. Regardless of minor potency variations, ivermectin, moxidectin and doramectin have a common recommended dose rate in cattle (200 mcg/kg). In dogs, for efficacy against larval stages of *Dirofilaria immitis*, commercial dose rates
for ivermectin, moxidectin and milbemycin oxime are 6 mcg/kg, 3 mcg/kg and 500 mcg/kg respectively.

**References:**
