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## **Synthetic Acaricides in Tick Control Programs: An Overview of Present Applications**

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### **ABSTRACT**

Ticks are a large group of blood-feeding arthropods that act as vectors for a range of pathogens of medical and veterinary importance. Historically, synthetic acaricides have been the cornerstone of global tick control efforts. Consequently, it is essential to develop strategies that help maintain the effectiveness of these chemicals. This paper provides an overview of synthetic acaricides, tracing their use from early applications to current market options. It also examines the mechanisms of action of different acaricide classes, their environmental impact, the challenges posed by resistance in tick populations, the factors contributing to this resistance, and the strategies implemented to increase the effectiveness of existing acaricides.

**Keywords:** Synthetic acaricides, Mode of action, Acaricide resistance, Resistance management

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### **Introduction**

Ticks are specialized arthropods that are obligate blood-feeders, drawing nourishment from a diverse range of vertebrates worldwide [1, 2]. Known for their significant role in transmitting numerous life-threatening diseases, they also pose considerable challenges as pests for both humans and livestock [3, 4]. Domestic animals, which are particularly vital for rural communities in developing countries, provide essential resources such as income, food, energy, manure, and raw materials [5]. However, tick infestations are a major threat to these animals, causing global losses estimated at between US\$ 13.9 and 18.7 billion each year [6]. As a result, tick control became a critical concern in both the public and animal health sectors.

The primary method for controlling ticks has traditionally been the usage of synthetic acaricides, offering a relatively efficient and cost-effective means to manage tick populations during outbreaks. However, prolonged usage of these chemicals has led to the development of resistance in numerous tick species, diminishing their effectiveness [7, 8]. Consequently, it is vital to regularly monitor ticks for resistance to commonly used acaricides to ensure the sustainability of livestock production. This paper explores the various aspects of synthetic acaricides, aiming to enhance the understanding and formulation of strategies to combat resistant tick species.

### **Results and Discussion**

#### *Synthetic acaricides*

Before the discovery by Smith and Kilborne of ticks as vectors of *Babesia bigemina* in cattle, chemical agents for tick control were already in use in regions like the United States, Southern Africa, and Australia [9-11]. In the U.S., early methods included applying mixtures of lard and sulfur, fish oil, lard, kerosene, or cotton-seed oil to

cattle's legs and bodies. Other combinations, such as kerosene mixed with cotton-seed oil and sulfur, or crude petroleum with cotton-seed oil, were also used effectively. These treatments were applied 2-3 times a week with syringes, brushes, brooms, sponges, or mops [12, 13]. Meanwhile, in Australia, dipping vats containing oil and "carbolics" were employed by researchers in 1895 to immerse cattle as part of their tick control practices [14].

#### *Arsenicals*

Arsenicals were the first acaricides extensively used to manage ticks and tick-borne diseases. Their use in controlling sheep parasites predates their initial use on cattle in Southern Africa and Australia in 1893 and 1895, respectively [15]. Arsenic-based solutions were recognized for their affordability, stability, and water solubility [16], making them both economical and highly effective [17]. These solutions were particularly utilized in controlling *Boophilus* tick species in countries such as South Africa, Australia, Brazil, Argentina, Colombia, Kenya, and Zambia [17].

However, after a few years, instances of field failures began to emerge. The first signs of arsenic resistance in Australia were observed in *Boophilus microplus* in 1937. Similar cases of resistance were reported in South Africa in species such as *Boophilus decoloratus*, *Amblyomma hebraeum*, *Hyalomma rufipes*, *H. truncatum*, *Rhipicephalus appendiculatus*, and *Rhipicephalus evertsi* [18]. As no alternative acaricides were available, tick infestations on cattle surged significantly worldwide. The development of resistance to arsenicals, along with the narrow margin between effective and toxic concentrations for both ticks and cattle, along with concerns over toxic residues in animal tissues, led to the eventual replacement of arsenic by synthetic organic insecticides following World War II [19].

#### *Organochlorines*

Organochlorines were the first synthetic organic insecticides introduced for tick control in cattle. These compounds offered broad-spectrum activity, high efficiency, and long-lasting residual effects. Compared to arsenic-based acaricides, they were also less toxic and more cost-effective [20]. Among the most notable organochlorines were benzene hexachloride [16] and DDT [21-23]. The widely used chemicals in this category included dieldrin, aldrin, cyclodiene compounds, and toxaphene, a polychloroterpene product [18]. The substances functioned by binding to the picrotoxinin site within the  $\gamma$ -aminobutyric acid (GABA) chloride ionophore complex [24, 25], disrupting chloride ion flow into neurons [26, 27]. This interference impaired the GABA-ergic inhibitory neurons, leading to excessive neural excitation and ultimately causing tick mortality.

The first recorded case of organochlorine resistance in *B. microplus* occurred in Brazil in 1952 [28]. The emergence of cross-resistance among different tick species, including *B. microplus*, *Boophilus decoloratus*, and *R. appendiculatus*, significantly reduced the effectiveness of these chemicals [18]. This resistance issue led to a decline in their use across regions such as Australia [29, 30] and parts of Equatorial and Southern Africa [31, 32]. By 1962, nearly all organochlorines were banned for tick control due to their persistent residues in meat, milk, and the environment, as they exhibited poor biodegradability and strong lipid affinity [33]. However, recent *in vitro* studies on lindane's effects on engorged female *Rhipicephalus (Boophilus) annulatus* and *Haemaphysalis bispinosa* demonstrated its efficacy as an acaricide. Despite causing high mortality, reduced fecundity, and hindrance in egg hatching, its use remains prohibited in India [34].

#### *Organophosphates and carbamates*

With the rise of resistance in tick species against organochlorines, a new category of organic insecticides, known as organophosphates, was developed. These compounds were initially examined for their pesticidal properties in the 1930s based on their effects on the nervous system. The first organophosphate, parathion, was introduced in the 1940s, and by the mid-1950s, organophosphates gradually replaced organochlorines in South America as tick populations became resistant to the latter [33, 35]. Unlike organochlorines, which were highly persistent in the environment, organophosphates were chemically unstable and degraded more quickly. However, they posed a higher risk of acute toxicity to livestock [16]. These acaricides were specifically designed to combat organochlorine-resistant *Boophilus* ticks, which were widespread in cattle-rearing regions across the tropics and subtropics [36]. In Australia, organophosphates were the dominant tick control agents from the 1950s until the late 1960s and early 1970s. Similarly, Mexico's national tick eradication program (1974-1984) relied heavily on organophosphates [37]. During this period, the most commonly used compounds included coumaphos, chlorpyrifos, diazinon, chlorfenvinphos, and ethion.

Alongside organophosphates, another class of chemicals known as carbamates was introduced in the mid-1950s. These compounds, which were esters of carbamic acid, closely resembled organophosphates in their mode of action [38]. Both groups of acaricides, including examples like carbaryl and promacyl, functioned by inhibiting AChE, an enzyme essential for nervous system function [18, 39-41]. When ticks were exposed to cholinesterase inhibitors, the enzyme could no longer break down acetylcholine, leading to continuous neural stimulation, overexcitation of the nervous system, and ultimately, tick mortality [42]. However, compared to organophosphates, carbamates were more toxic to mammals and significantly more expensive [17].

Despite their initial effectiveness, the widespread reliance on organophosphate-carbamate acaricides eventually led to resistance in multiple tick species. The first reports of resistance in *B. microplus* appeared in Australia during the mid-1960s [43]. Soon after, resistance to this class of chemicals was documented in several other species, including *B. decoloratus*, *A. hebraeum*, *R. appendiculatus*, and *Rhipicephalus evertsi* in South Africa. Resistant strains of *B. microplus* were later reported in Brazil, South America, Mexico, Colombia, Uruguay, Argentina, and Venezuela [18]. As a result, the use of organophosphates declined across North America and European Union nations during the 1970s [44]. A similar reduction occurred in Australia, large parts of Africa, and various Latin American regions [45]. Nevertheless, certain organophosphates continue to be used in veterinary and public health applications due to their targeted efficacy. For instance, coumaphos remains a key active ingredient in the acaricide officially sanctioned by the U.S. Cattle Fever Tick Eradication Program for livestock treatment [46].

#### *Formamidines*

By the mid-1970s, as the organophosphate-carbamate group of acaricides failed to effectively control tick populations, they were replaced by amidines [47]. This category included compounds such as chlordimeform, clenpyrin, amitraz, chloromethiuron, and cymiazole [48]. In Australia, chlordimeform was initially introduced as a supplement to organophosphates in cattle dipping vats to restore their effectiveness against resistant tick strains [47]. However, due to concerns over its carcinogenic properties, it was withdrawn from the market in 1976 [49]. Among the chemicals in this class, amitraz, a triazapentadiene compound, became the primary active ingredient widely used for tick control in livestock and dogs [44]. Amitraz acted as an octopamine agonist, disrupting the nervous system of arachnids and leading to their demise [50].

Commercially available amitraz formulations proved effective against organophosphate-resistant *B. microplus* and were widely adopted in Australia during the mid-1970s for cattle treatment [18, 51]. Extensive trials conducted in South Africa over five years confirmed amitraz's effectiveness in managing *B. decoloratus*, *R. appendiculatus*, *R. evertsi*, and *A. hebraeum* populations [52]. However, resistance to amitraz began emerging 4-10 years after its introduction, with the first documented cases appearing in Australia in the early 1980s [47]. Subsequent reports of resistance surfaced from Mexico, South America, New Caledonia, South Africa, Brazil, and Colombia [18]. Despite these challenges, Jonsson and Hope [53] highlighted that amitraz remained one of the most commonly used acaricides for tick control in regions such as Australia, Latin America, and Southern Africa [54].

#### *Pyrethroids*

Pyrethroids emerged in the late 1970s as a solution for tick populations resistant to amidines. These synthetic compounds were developed as stable alternatives to natural pyrethrum, which degraded quickly in sunlight. Though research on pyrethroids began in 1949, the third-generation chemicals, permethrin and fenvalerate, were the first to be widely used for tick control. In the 1970s, the US Environmental Protection Agency (EPA) approved permethrin and deltamethrin as acaricides. Other widely used pyrethroids include cypermethrin, flumethrin, cyhalothrin, and cyfluthrin [55, 56]. They disrupted sodium ion channels in nerve membranes, leading to nerve excitation and paralysis in ticks [42, 57, 58].

By the early 2000s, pyrethroids made up 17% of the global insecticide market [59]. Flumethrin proved particularly effective at lower concentrations compared to other pyrethroids [60]. Studies showed that trans-flumethrin was significantly more toxic to *B. microplus* than cis-cypermethrin and deltamethrin [61]. Although pyrethroids had lower toxicity to mammals and birds, their widespread use led to environmental concerns due to urban runoff, which posed risks to aquatic organisms.

#### *Macrocyclic lactones*

Introduced in 1981, macrocyclic lactones offered a long-lasting and effective tick control method [62]. These compounds had greater residual activity than synthetic pyrethroids and targeted a broad range of arthropods and nematodes [55]. Macrocyclic lactones fell into two categories: avermectins, derived from *Streptomyces avermitilis*, and milbemycins, obtained from *Streptomyces hygroscopicus aureolacrimosus* [63]. Key acaricides in this group included ivermectin, eprinomectin, doramectin, and moxidectin.

These chemicals worked by increasing gamma-aminobutyric acid (GABA) release, which blocked nerve and muscle function in ticks, ultimately causing paralysis and death [64-66]. Subcutaneous treatments with ivermectin, doramectin, and moxidectin effectively controlled *B. microplus* infestations in cattle. However, their high cost restricted widespread use [67-69]. The first report of macrocyclic lactone resistance in *B. microplus* came from Brazil in the early 2000s [18].

#### *Phenylpyrazoles*

Discovered in the 1980s, fipronil was the first acaricide in the phenylpyrazole class, initially developed for crop protection. Later, it was tested as a pour-on treatment for cattle infested with *B. microplus*. In controlled environments, a single application provided over 99% efficacy and protected against larval reinfestation for up to eight weeks [70]. However, under field conditions, factors like sunlight and weather exposure reduced its long-lasting effects by two to three weeks [71]. While fipronil is used in several Latin American countries for tick control, it has not been registered for use on food animals in the United States and some other regions.

#### *Benzoylphenylurea*

Diflubenzuron was the first benzoyl phenyl urea acaricide, approved in Brazil as an oral treatment for *Rhipicephalus (Boophilus) microplus* infestations. Most compounds in this group, including diflubenzuron, lufenuron, and flufenoxuron, were effective against various insects. However, fluazuron stood out due to its high efficacy against ticks and some mite species [55]. Marketed as a tick development inhibitor, fluazuron was available as a pour-on formulation, offering long-term protection against *R. microplus* [72]. It significantly reduced the reproductive capacity of engorged female ticks and increased immature tick mortality by disrupting molting. The effects of fluazuron lasted around twelve weeks. Because of its strong fat-binding properties, it was excreted in milk, making treatment unnecessary for suckling calves. Due to its persistence in fat, a six-week withdrawal period was required before treated cattle could be used for human consumption [72].

#### *Spinosad*

Spinosad belongs to the spinosyn class of pesticides, which are tetracyclic-macrolide compounds derived from the fermentation of soil bacteria in the *Saccharopolyspora* genus [73, 74]. Its mode of action involves interfering with acetylcholine binding at nicotine acetylcholine receptors in the postsynaptic cell [49]. As a systemic acaricide, spinosad has been effectively used as an oral treatment in dogs to manage *Rhipicephalus sanguineus* infestations [75]. Research on its efficacy against both hard and soft ticks highlights its potential as an alternative to conventional acaricides used for vector and pest control in public health [76]. Spinosad demonstrated around 90% effectiveness in controlling *B. microplus* on cattle across all three parasitic stages at the time of treatment. Nymphs and larvae were particularly susceptible compared to adult ticks [77]. Given its distinct mechanism of action, spinosad offers a viable alternative for managing *B. microplus* populations resistant to other acaricides [18].

#### *Resistance management strategies*

Chemical acaricides remain the primary method for tick control, but their effectiveness has declined over time [78]. The widespread and uncontrolled use of these chemicals, errors in solution preparation, improper application techniques, incorrect timing, and poor parasite management have all contributed to the emergence of resistance among tick populations commonly targeted by cattle producers [79]. While completely preventing resistance in tick control programs is unrealistic, certain strategies can help slow its development. Additionally, alternative approaches may be considered when resistance renders specific acaricides ineffective [80].

#### *Application practices*

Selecting an appropriate acaricide requires a thorough understanding of the tick species present in the affected area and their resistance to different chemicals. Factors such as application method [81], dosage, frequency, and

treatment timing [82] should be carefully considered to slow resistance development. Frequent use of acaricides accelerates resistance, and earlier research by Jonsson *et al.* [81] and Thullner *et al.* [83] advised limiting applications to no more than five times per season. Additionally, Sun *et al.* [84] recommended confirming field resistance through laboratory testing alongside established management practices.

#### *Rotation of acaricides*

Alternating acaricides with different mechanisms of action can help mitigate resistance development [42]. Prolonged use of a single acaricide leads to the dominance of resistant alleles, eventually causing treatment failure [44]. In a laboratory study by Thullner *et al.* [83], a highly deltamethrin-resistant *R. microplus* strain showed reduced resistance when deltamethrin was rotated with coumaphos. Similarly, Jonsson *et al.* [85] observed a decline in amitraz resistance when cattle were treated alternately with spinosad and amitraz. However, further field research is necessary to confirm the effectiveness of this approach.

#### *Using acaricide combinations*

Using combinations of acaricides with different modes of action reduces the likelihood of resistance developing against both chemicals [86]. This strategy has been implemented in several countries. In Australia, organophosphate-synthetic pyrethroid combinations, including deltamethrin + ethion and cypermethrin + chlorfenvinphos, have remained available [18]. Similarly, in Brazil, cypermethrin + chlorfenvinphos and permethrin + dichlorvos have been commonly used [87]. In Mexico, cymiazole + cypermethrin is a widely applied mixture [88]. Recent findings by Santana [89] demonstrated that cypermethrin (15%) + chlorpyrifos (25%) + citronellal (1%) was more effective against *Rhipicephalus (Boophilus) microplus* than pyrethroids or organophosphates alone.

#### *Use of synergists*

Certain acaricides exhibit synergistic effects when combined. Piperonyl butoxide has been used alongside pyrethroids to enhance their efficacy against resistant tick populations. Li *et al.* [90] observed synergy between permethrin and amitraz, while Fernandez-Salas *et al.* [91] found that combining amitraz with permethrin effectively controlled a pyrethroid-resistant *R. microplus* strain in Mexico. However, these combinations must be carefully formulated and applied at recommended concentrations to ensure compatibility and persistence [42].

#### *Tick pheromones in combination with acaricides*

Ticks respond to semiochemicals that influence behaviors such as aggregation, attachment, and mating. Exploiting these pheromones in control strategies could enhance acaricide effectiveness [92, 93]. While pheromones alone are insufficient for tick management, their combination with acaricides—ideally in a slow-release delivery system—could improve results. Technologies such as embedding pheromones in plastic, adhesives, paraffin, or gelatin microcapsules enable gradual release. A field study using assembly pheromone + toxaphene effectively controlled *A. hebraeum* [94]. Sonenshine *et al.* [95] reported high *Dermacentor variabilis* mortality when propoxur was combined with the sex pheromone 2,6-dichlorophenol on dogs, while Sonenshine *et al.* [96] found that *Ixodes scapularis* treated with permethrin and an arrestant pheromone showed 95% mortality in laboratory tests. Combining pheromones with acaricides could improve treatment efficiency and reduce the impact on non-target species.

## **Conclusion**

Ticks and the diseases they transmit pose a significant risk to both human and animal health worldwide. Managing tick populations has become a top priority for public and veterinary health systems, with acaricides serving as a key tool in effective control strategies. During sudden outbreaks, chemical acaricides remain the primary solution due to their rapid and efficient action. However, concerns related to resistance development, the need for safer formulations, and their environmental impact are influencing how these chemicals are used. History has shown that resistance to acaricides is inevitable, making long-term tick control dependent on continuous research and innovation. Future efforts must focus on developing novel, lower-risk acaricides and implementing integrated management strategies to ensure sustainable control.



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