LETTER TO THE EDITOR

Ivermectin use on pastured livestock in Colombia: parasite resistance and impacts on the dung community

Uso de ivermectina en ganado en pastoreo en Colombia: resistencia parasitaria e impacto en la comunidad de estiércol

Uso de ivermectina em gado a pasto na Colômbia: resistência parasitária e impacto na comunidade de esterco

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Abstract

Ivermectin (IVM) has been the most widely used antiparasitic agent in veterinary medicine since it came to the market in 1981. In its risk assessment, the American Food and Drug Administration (FDA) determined that, although it is very toxic to aquatic organisms, it is unlikely to contaminate watercourses from current applications registered for animal use. However, the effects of IVM on non-target invertebrate fauna can greatly impact grassland ecology. The economic loss from undegraded dung on lowering the quality of pastures and reducing the area of pasture available and palatable to livestock was US $380 million for the American economy in 2003. We discuss selected aspects of IVM effects on non-target species, dung beetles in pastures. We do not consider confined or feedlot production. Ivermectin affects a highly beneficial and taxonomically diverse group inhabiting dung pats, including flies, parasitic wasps, and coprophilus and predatory dung beetles. Some studies show that dung from IVM-treated animals can remain in the pasture without noticeable signs of degradation for up to 340 days, while pats from untreated animals are almost completely degraded after 80 days. Field and laboratory studies have shown many invertebrates species are susceptible to IVM at concentrations well below those excreted in the feces of treated cattle. IVM affects reproduction and development of coleopteran larvae at concentrations up to 10 times lower that cause mortality. In Colombia, at least 68 species of the subfamily Scarabaeinae have been identified in dung communities. Greater diversity of dung beetles is associated with forests and silvopastoral systems that incorporate native trees and provide habitats for survival. IVM should be used selectively on animals on pasture to minimize parasite resistance and effects on dung beetle communities and other nontarget invertebrate communities.

Keywords: *coprophagous beetle; dung; dung-associated invertebrates; dung beetle; dung insect; ivermectin; manure beetle; parasite resistance.*

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Resumen

La ivermectina (IVM) ha sido el agente antiparasitario más utilizado en medicina veterinaria desde que llegó al mercado en 1981. En su evaluación de riesgos, la Administración Americana de Alimentos y Medicamentos (Food and Drug Administration) determinó que, aunque es muy tóxico para los organismos acuáticos, es poco probable que contamine los cursos de agua con las aplicaciones actuales registradas para uso animal. Sin embargo, los efectos de la IVM en la fauna de invertebrados no destino pueden tener un gran impacto en la ecología de los pastizales con altos costos asociados a la presencia de estiércol no degradado. La pérdida económica de la disminución de la calidad de los pastos y la reducción del área de pastos disponibles y apetecibles para el ganado se ha estimado en US $380 millones para la economía estadounidense. La ivermectina afecta a un grupo altamente beneficioso y taxonómicamente diverso que habita en las boñigas, incluidas moscas, avispas parásitas y los escarabajos coprofilos y depredadores. Algunos estudios muestran que las boñigas de animales tratados con IVM puede permanecer en el pasto sin signos notables de degradación hasta por 340 días, mientras que las de animales no tratados se degradan casi por completo después de 80 días. Además, estudios de campo y de laboratorio han demostrado que la susceptibilidad de muchos insectos ocurre a concentraciones muy por debajo de las excretadas en las heces del ganado tratado con IVM. Los efectos sobre la reproducción y el desarrollo de las larvas de coleópteros ocurren a concentraciones que pueden ser 10 veces más bajas que las que causan mortalidad. En Colombia, se han identificado al menos 68 especies de la subfamilia Scarabaeinae en comunidades de estiércol. La mayor diversidad de escarabajos se ha asociado con bosques y sistemas silvopastoriles que incorporan árboles nativos y proporcionan hábitats para su supervivencia.

Palabras clave: *boñigas; bovino; escarabajos; escarabajo coprófago; escarabajo estercolero; insectos del estiércol; invertebrados asociados al estiércol; ivermectina; parásitos; resistencia.*

Resumo

A ivermectina (IVM) tem sido o agente antiparasitico mais utilizado na medicina veterinária desde que chegou ao mercado em 1981. Em sua avaliação de risco, a American Food and Drug Administration (FDA) determinou que, embora seja muito tóxico para organismos aquáticos, é improvável contaminar os cursos d'água das aplicações atuais registradas para uso animal. No entanto, os efeitos do IVM na fauna invertebrada não-alvo podem impactar muito a ecologia das pastagens devido aos custos associados à presença de esterco não degradado. A perda econômica da redução da qualidade das pastagens e da redução da área de pastagem disponível e palatável para a pecuária foi estimada em US $380 milhões para a economia americana. A ivermectina afeta um grupo altamente benéfico e taxonomicamente diverso que habita pats de esterco, incluindo moscas, vespas parasitas e besouros coprophilus e de esterco predatório. Alguns estudos mostram que esterco de animais tratados com IVM pode permanecer no pasto sem sinais visíveis de degradação por até 340 dias, enquanto os tapinhas de animais não tratados são quase completamente degradados após 80 dias. Além disso, estudos de campo e laboratório têm demonstrado a suscetibilidade de muitos insetos ocorrerem em concentrações bem abaixo daquelas excretadas nas fezes de bovinos tratados com IVM. Os efeitos na reprodução e desenvolvimento de larvas coleopteranas ocorrem em concentrações 10 vezes menores do que aquelas que causam mortalidade. Na Colômbia, pelo menos 68 espécies da subfamília Scarabaeinae foram identificadas em comunidades de esterco. A maior diversidade de besouros de esterco tem sido associada a florestas e sistemas silvopastorais que incorporam árvores nativas e fornecem habitats para sobrevivência.

Palavras-chave: *besouros; besouro coprófago; besouros de estrume; boñigas; bovina; invertebrados associados ao esterco; ivermectina; resistência; parasitas.*

Introduction

Ivermectin (IVM) has been the most widely used antiparasitic in veterinary medicine worldwide since it came to market in 1981. It has been used by all routes of administration and in all domestic animal species to treat both internal and external parasites (endectocide). Macrocyclic lactones, including IVM, act on glutamate and GABA ionic receptors, a common mechanism for all ecdysozoans, constituting a superphylum within the animal kingdom (Figure 1). All ecdysozoans share a three-layer cuticle which is periodically molted as the animal grows, a process called ecdysis that gives the group its name. It includes several phyla, of which the most representative are arthropods and nematodes.

Results

History

An environmental impact assessment by the US FDA concluded that although IVM is very toxic to crustaceans (i.e., *Daphnia magna*) and fish, it is unlikely that the applications registered for animal use would contaminate watercourses from runoff of fertilized or contaminated pastures (Bloom and Matheson, 1993). The FDA´s conclusion was based on the low water solubility of IVM (4 ppm), strong adhesion to soils and sediments (Koc = 12,660-15,700), and rapid degradation in water (half-life of 12 to 39 hours). In contrast, a European risk assessment using a tiered approach with many more organisms concluded that risk to aquatic and terrestrial organisms is unacceptable; therefore, measures should be implemented to mitigate contamination of each environmental compartment studied (Liebig *et al.*, 2010).

IVM administered parenterally or topically to animals in agriculture and aquaculture is excreted virtually intact with feces (Horvat *et al.*, 2012). Peaks range between 2 and 7 days after parenteral or topical application, followed by a long decreasing excretion in the next 4 to 6 weeks. Excreted parent IVM and metabolites can affect the entire community of insects that inhabit and/or reproduce in livestock dung pats, with effects that can be conflicting.

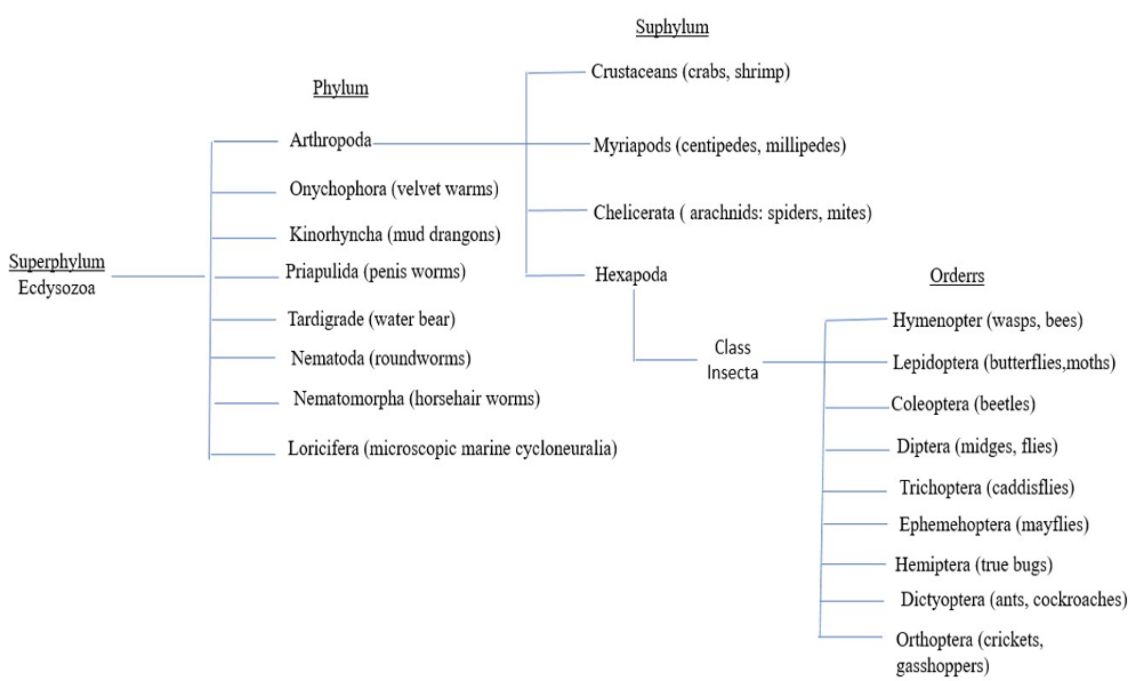

Figure 1. Classification of taxons within the superphylum Ecdysozoa affected by ivermectin. Nine of 30 orders of insects are in this figure.

On the one hand, excreted compounds could reduce the population of species considered pests that develop on dung pats (i.e., *Haematobia irritans, Musca autumnalis, Stomoxys calcitrans*). On the other these compounds can affect populations of beneficial insects that degrade dung, particularly coprophilous and predatory beetles in the Scarabaeidae, Hydrophilidae, and Staphylinidae families. A study that assessed the effects of different concentrations of ivermectin reported that increasing concentrations of ivermectin correlate with a lower abundance and diversity of different insect species (Floate *et al.*, 2015). Up to 450 species of arthropods have been found in dungs (Floate, 2011), of which beetles (Coleoptera) are the most important dung pat degraders.

Degrading dung from the paddocks can reduce pest flies by up to 80% (Dadour and Allen, 2001). Degraders enable faster renovation of pastures by recycling nutrients and aeration of the soil. If dungs do not decompose, the pasture area could be reduced by 4.8% each year (Beynon *et al.*, 2012). Dung beetles saved American livestock production $380 million in 2003 (Losey and Vaughan, 2006), equivalent to $580.6 million US $ and 22.8 billion COP in 2022. These benefits for dung beetles were calculated based on less pollution of pastures, less volatilization of nitrogen (wet dungs in paddocks lose up to 80% of their nitrogen in the form of ammonia until they dry), and a decrease in parasitism and pest flies. Total ecological services insects provided in the United States was ≥57 billion in 2003 US$ (Losey and Vaughan, 2006). The economic importance of dung beetles is so great that Australia funded a program (1968 to 1986) that introduced 55 exotic dung beetle species from Africa and Europe to accelerate the degradation of dungs (Doube and Macqueen, 1991).

One of the first studies that assessed the effect of intraluminal boluses of ivermectin on the persistence of dung pats in the environment showed a large difference in decomposition at 20, 40, 60, 80, and 100 days (Wall and Strong, 1987). At 100 days post-deposition, dung from controlled cattle had disappeared, whereas those of treated animals were largely intact. In control animal pats, beetles (including larvae, pupae, and adults) accounted for 78.8% of all identified invertebrates, followed by Diptera (18.3%) and worms (2.8%.) The Scarabaeidae family was the most numerous (89.4%). A subsequent study determined that fecal IVM concentrations of 400 ppb following intraruminal administration of IVM boluses killed all beetle larvae species for 4-5 months (Strong and Wall, 1988). Dung pats spiked with IVM had hardly any signs of degradation within 340 days of staying in pastures, while those of untreated cattle had degraded by about 80% after 80 days in a pasture (Floate, 1998).

One way used to assess the effect of IVM on the dung community is the time it takes for adult insects to appear after dungs are left on the pasture for 1-2 weeks to allow their colonization. Dungs are collected fresh (<3 hours post-defecation) and kept frozen until used. They are then exposed on isopor cell culture plates in different areas of the pasture. Once exposed for 1-2 weeks, they are collected and kept in cages protected by meshes until the adults emerge and are counted and identified (Floate, 1998). Dung pats from animals treated with topical ivermectin 12 weeks earlier had fewer adult insects emerge from various taxa: coprophagous flies, predatory wasps, and coprophagous and predatory beetles (Figure 2). The species selected in Figure 2 represent some of the main species of 75 species in 28 distinct families, that were identified.

A recent study of beetle fauna throughout Colombia reported that of 11,255 specimens, 19 genera were from the subfamily Scarabaeinae, with 42 different species (Medevil-Nieto *et al.*, 2020). A study in forests that collected 11,686 beetles found 18 genera and 68 species, all of them from the family Scarabaeinae (Gonzalez-Alvarado *et al.*, 2015). The fauna of different insects associated with cattle dungs in Colombia is shown in Figure 3. A guide describes the ideal conditions for beetles to colonize different areas according to the types of habitat or ecoregions of Colombia (Giraldo *et al.*, 2018). The forests of each region are the natural habitat of beetles, so the guide concludes that tree cover should be provided because deforestation hinders the survival of many species.

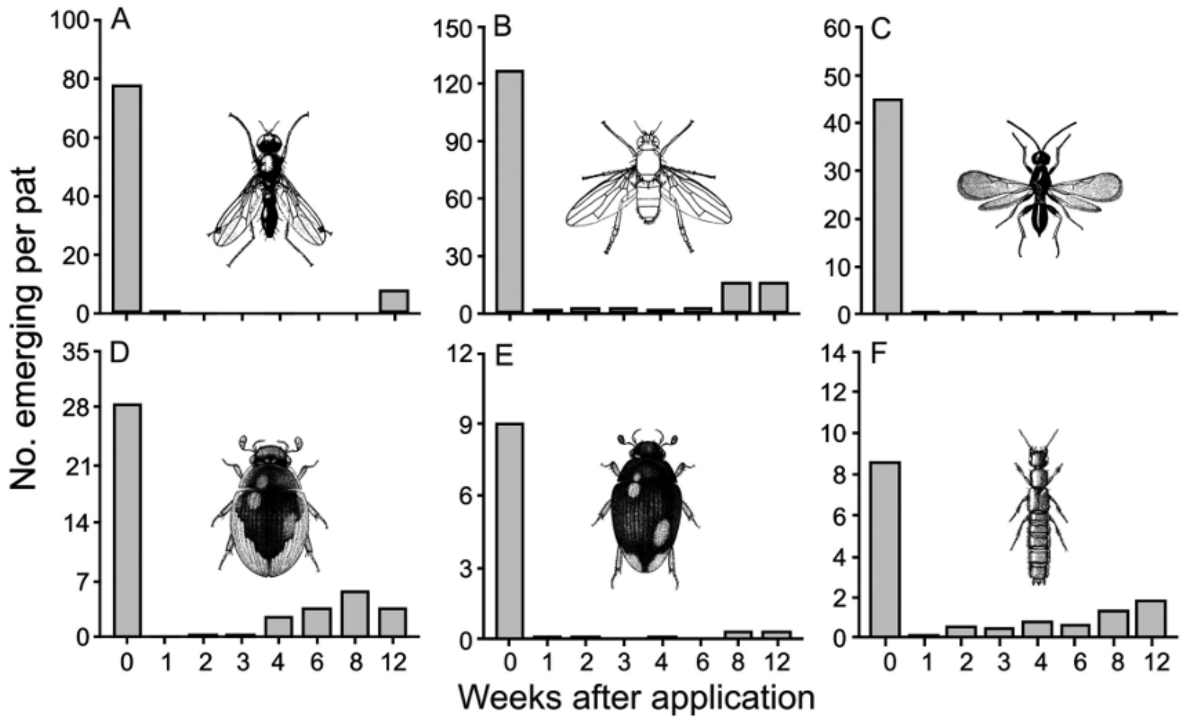

Figure 2. The emergence of insects developing in dung pats from untreated cattle (treated for 0 wk) versus dung from cattle treated 1 to 12 wk previously with a topical dose of IVM (500 µg/kg body weight). A, B, dung-feeding flies *Sepsis* spp. and *Coproica mitchelli*, respectively. C, parasitic wasps (Eucoilidae). D, E, dung-feeding beetles *Cercyon pygmaeus* and *C. quisquilius*, respectively. F, predaceous beetle *Aleocharinae* sp. Values are means for 12 pats per Interval. Adapted from Floate (1998) and Giraldo-Echeverri *et al.*, (2018).

In forests and silvopastoral systems with shade and leaf litter coverage, the temperature is considerably reduced, and the relative humidity is increased, generating optimal conditions for most species of manure beetles. A study in three different natural systems of the Cesar River Valley found 28 species in native forest areas, 18 species in silvopastoral systems, and 10 species in treeless pastures (Montoya-Molina *et al.*, 2015).

Parasite resistance to IVM in Colombian studies

In the last decade, numerous studies reported great resistance of the parasites that are tried to control with IVM. Our group has demonstrated with *in vivo* and *in vitro* tests that farmers' claims that acaricidal products (including IVM) have lost their effectiveness in controlling the bovine tick, *Rhipicephalus microplus*, are valid (Chaparro *et al.*, 2019; Lopez-Arias *et al.*, 2014; Puerta *et al.*, 2015; Villar *et al.*, 2016a; 2016b; 2020;). Resistance manifests in two practical aspects: 1) a reduction in the number of ticks that should disappear after treatment with IVM, and 2) a decrease in the duration of the effect to what the insert claims. In some farms, the resistance was equal to or greater than the worst-case reported in other countries. For example, on two farms, the resistant population was about half of all ticks based on discriminatory doses similar to LC50 and tick counts at 10 post-administration IVM (Chaparro *et al.*, 2019). Both farms used IVM for years in 100% of the animals at two-month intervals. An illegal product (Ivercyt) without ICA (Instituto Colombiano Agropecuario) registration containing 10.5% IVM, three times the legal product (3.15%), was also used (Lopez-Arias *et al.*, 2014). On the other hand, those farms in which ticks have been susceptible reported that the use of IVM did not exceed 2 annual treatments (Chaparro *et al.*, 2019).

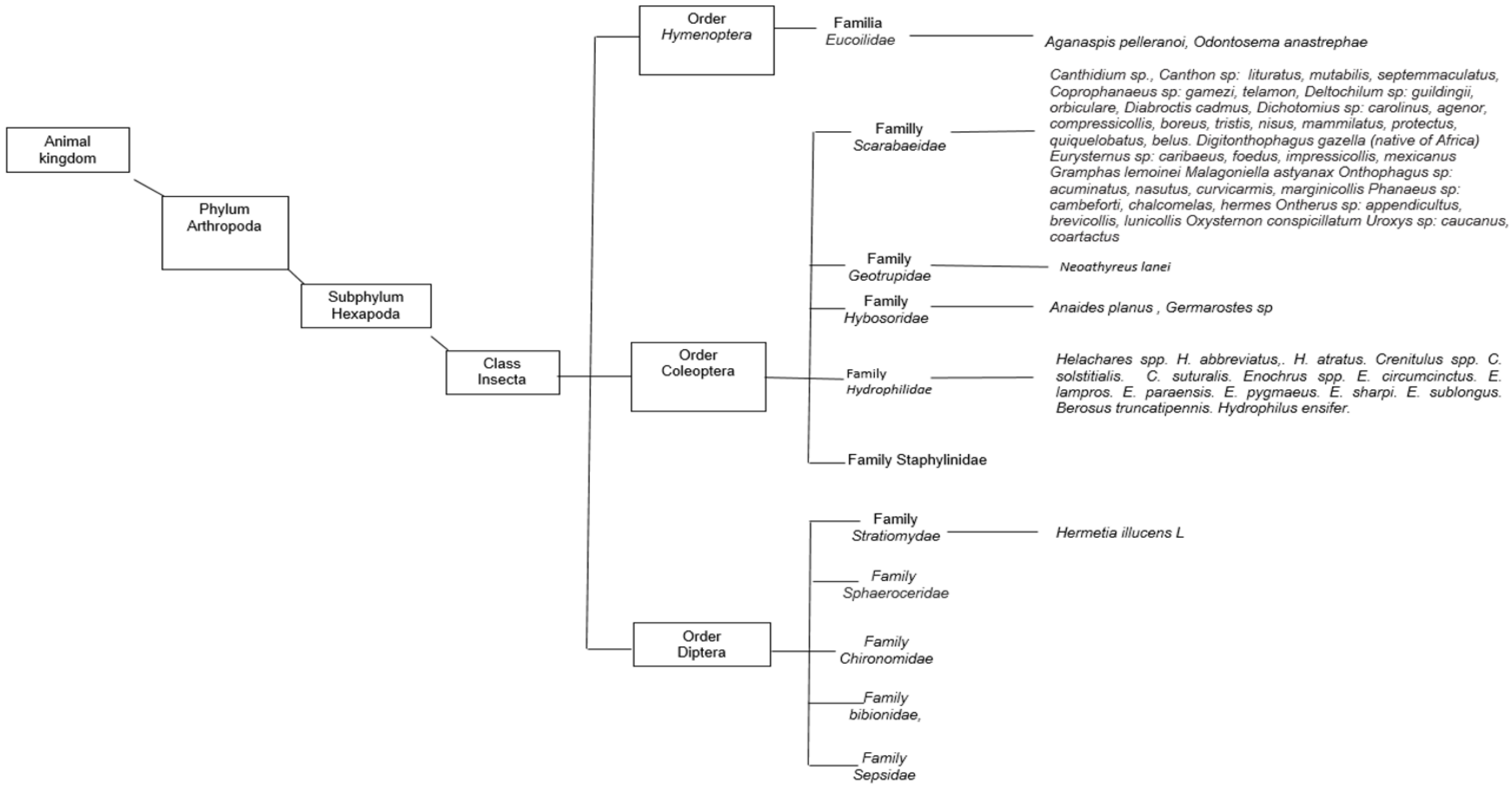

Figure 3. Insects identified in dung pats in Colombia (only those quoted with reference). Notice the lack of studies in the orders Diptera and Hymenoptera. Most studies have concentrated on the Family Scarabaeidae.

Studies in 5 sheep and goat farms confirmed the presence of multidrug-resistant *Haemonchus contortus* to three classes of anthelmintics, including macrocyclic lactones (unpublished observations). Specifically, in one of the farms with great mortality of lambs and females in the peripartum period, the total resistance of *Haemonchus contortus* to albendazole, ivermectin, and levamisole was verified (Chaparro *et al.*, 2017). The study assessed resistance *in vivo* by the fecal egg reduction test at 10 days of treatment compared to an untreated control group and the *in vitro* DrenchRite® Larval Development Assay. Only moxidectin produced a post-treatment egg count reduction of 76.7%.

Discussion

IVM has been considered a safe antiparasitic based on its low toxicity in mammals and birds. The main environmental effect of the IVM has focused on the fauna of the dung pat, which by favoring its rapid degradation, is economically and functionally important for pastures; if this does not happen, farmers could suffer significant economic losses due to pasture contamination, increased parasitic fly populations and increased transmission of endoparasites. The risk assessments conducted by regulatory agencies have reached different conclusions. The American FDA concluded the risk to populations of insects using the dung pats is low and transient; the European Agency for the Assessment of Medicines concluded there is a great risk to the fauna of the dung pat critical for its decomposition in the environment, and dangerous for aquatic organisms if it reaches waterways. To this end, measures to mitigate the possible impact include preventing the access of treated animals to watercourses when they are expected to excrete IVM residues with feces.

Similarly, the impact on the dung pat community could be reduced by implementing comprehensive parasite combat practices that reduce the number of applications of IVM (and other macrocyclic lactones) and thus reduce exposure to non-target species. Current preventive practices of treating 100% of the animals in a herd, with short intervals between applications, increase exposures to non-target species and resistance in target species. Many countries have guidelines for the sustainable management of parasites focused on combating resistance to antiparasitics.

In conclusion, treatment should target individual animals that need treatment and when they need it. For example, fecal egg counts of helminths should be done and animals treated when a threshold count compromising health is reached. Typically, only young animals in a herd benefit from deworming. Another measure is to concentrate the animals to be treated in a restricted space during the IVM excretion period for each formulation and dispose of their toxic excrement as compost. The ideal approach is the holistic management of livestock that minimizes the need for pesticides and antiparasitic products. In that respect, silvopastoral systems with native evergreen broad-crown trees and shrubs should be encouraged because they generate a good amount of leaf litter to maintain soil cover and provide favorable habitats for native beetle species in livestock landscapes. A 2021 study of the effects on dung beetles from removing grazing cattle from Brazilian pastures suggested removal of cattle to grazing rotational management for one months (Correa *et al.*, 2021). We concur with this suggested strategy to conserve the diversity and ecological services of dung beetles in pastures.

Declarations

Conflicts of interest

The authors declare they have no conflicts of interest with regard to the work presented in this report.

Author contributions

Both authors: Conceptualizing, writing, critical review, and editing.

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