



Effects of Avermectins on the Environment Based on Its Toxicity to Plants and Soil Invertebrates—a Review

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Abstract Avermectins are pharmaceutical drugs widely used mainly in livestock to combat both ectoparasites and endoparasites. Drugs belonging to this family include ivermectin, abamectin, doramectin, selamectin, eprinomectin, and emamectin benzoate, and they share similar chemical characteristics. When administered to livestock, between 80 and 98% of the drug is estimated to leave the body without being metabolized in feces, thus reaching the soil. For this reason, concern for avermectin contamination in soil is increasing, and researchers are focused on estimating the effects on non-target organisms, such as plants and soil invertebrates. This review aimed to compile and discuss updated data of avermectin toxicity on non-target organisms to better comprehend its effect on the environment. Effects on plants are scarcely studied, since they were not believed to absorb these drugs. However, recent studies suggest that plants can be negatively affected. Regarding soil invertebrates, negative effects such as increased mortality and reduced reproduction are best known to dung-beetles. Recently, some studies have also suggested that earthworms, springtails, and enchytraeids can be adversely affected by avermectin exposure. Since ivermectin was the first avermectin marketed,

most of the data refers to this product. According to new data on scientific literature, avermectins can now be considered harmful to non-target organisms, and its prudent use is recommended in order to reduce negative effects on the environment. For future investigations, inclusion of avermectins other than ivermectin, as well as field and “omics” studies is suggested.

Keywords Ivermectin · Abamectin · Soil toxicity · Phytotoxicity · Earthworms · Dung beetles

1 Introduction

The avermectin (AVM) family, discovered in the 1970s, is currently regarded as one of the main drugs necessary to maintain world health and is included on the World Health Organization’s “List of Essential Medicines,” a compilation of the most important medications needed in any basic health system. Its discovery is considered exceptional, as AVM represented the world’s first “endectocide,” capable of killing a wide variety of both internal and external parasitic organisms in the body (Ōmura, 2016). In 2015, the scientists responsible for its discovery, William C. Campbell and Satoshi Ōmura, received the Nobel Prize in Physiology and Medicine for developing therapies that revolutionized the treatment of some of the most aggressive parasitic diseases (The Nobel Assembly, 2015).

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The characterization, isolation, production, and activity of these substances were first described by Burg et al. (1979), Egerton et al. (1979), and Miller et al. (1979). AVMs are produced by an actinomycete, originally named *Streptomyces avermitilis* MA-4680 and now called *Streptomyces avermectinius* (Takahashi et al., 2002), that was collected from soil samples in Japan and isolated by the Kitassato Institute. After several tests at Merck Sharp & Dohme Research Laboratories, the active ingredient responsible for endectocidal activity was identified and called “ivermectin,” which is a complex mixture of 16-membered macrocyclic lactones, where the fermentation of *S. Avermectinius* produces a mixture of eight AVM compounds (A1a, A1b, A2a, A2b, B1a, B1b, B2a, and B2b) (Ōmura, 2016). Further tests revealed that the 22,23-dihydro-B1 complex (a mixture of 80% B1a and 20% B1b) presented the most efficient endectocidal action and was therefore selected as the first AVM to be marketed under the name of ivermectin (Mectizan®) (Chabala et al., 1980).

AVMs were used therapeutically to treat only animals at first and were marketed for this purpose in 1981. Two years later, AVM became the top-selling veterinary product (Frost et al., 2002). The use in humans was approved in 1987, although promising results using low concentrations had already been observed by some researchers in treating onchocerciasis caused by the nematode *Onchocerca volvulus* (Aziz et al., 1982; Coulaud et al., 1983). From 1987 to 2014, the Mectizan Donation Program was responsible for donating 1.4 billion treatments for onchocerciasis control and elimination, and 1.2 billion treatments for the control of lymphatic filariasis (Mectizan Donation Program, 2014).

Currently, AVMs are widely used in agriculture as a veterinary medicine, particularly for the control of gastrointestinal roundworms, although they are also licensed to combat bovine lungworms and other ectoparasites (Laing et al., 2017) such as ticks (Benelli, 2016). Since parasitic infections can cause a reduction in livestock size and productivity, there is a strong financial incentive for producers to include such medicines in their management practices (Kovecses & Marcogliese, 2005). For this reason, AVMs are the most commonly used anthelmintics in sheep and horse breeding in the UK (Burgess et al., 2012; Relf et al., 2012; Stratford et al., 2014) and in the USA (Mcarthur & Reinemeyer, 2014). There

is also a large market for AVMs in the control of endo- and ectoparasites in domestic pets (Laing et al., 2017), and some researchers have demonstrated that AVMs limit infection from RNA viruses such as dengue (Tay et al., 2013), West Nile Virus (Yang et al., 2020), Venezuelan equine encephalitis virus (Lundberg et al., 2013), influenza (Götz et al., 2016), and SARS-CoV-2 in vitro (Caly et al., 2020).

Thus, the main method that AVMs enter the environment occurs through their administration in livestock (Fig. 1A). It is estimated that between 80 and 98% of the drug when administered to the animals can leave the body without being metabolized in feces, thus reaching the soil intact (Fig. 1B) (Horvat et al., 2012). When released into the environment, the fate of AVMs will depend on their physicochemical characteristics (low water solubility, nonvolatile, high affinity for lipids and organic matter). Accumulation in water is unlikely due to its low solubility (Halley, Nessel, et al., 1989), and their persistence and accumulation in soil depend on factors such as climate, soil type, and frequency of application in animals.

Despite the undeniable success of AVMs in combating both endo- and ectoparasites, concerns in the scientific community about their adverse effects, especially on non-target organisms (Fig. 1C and D), are rising. Since AVMs primarily reach the soil and are likely to accumulate in this compartment, this review aims to compile data from the literature on their toxicity to plants and invertebrates, organisms with an important role in maintaining ecological balance and which are primarily affected by soil contamination. Effects on plant species, dung-beetles, earthworms, springtails, and enchytraeids after exposure to AVM were collected from the scientific literature. These species were chosen due to their recognition as bioindicators of soil toxicity (ISO 11269–1, 2012a; ISO 11269–2, 2012b; ISO, 16387, 2012; ISO 11268–2, 2015; ISO, 11267, 2019).

2 Avermectin Derivatives

Naturally produced AVMs are a mixture of four complexes known as AVMs A1, A2, B1, and B2, and each complex has two homologues, “a” and “b,” for example B1a and B1b. The designations “A” and “B” refer to the presence of methoxy or hydroxy groups at position C5, while the numbers “1” and “2” indicate the

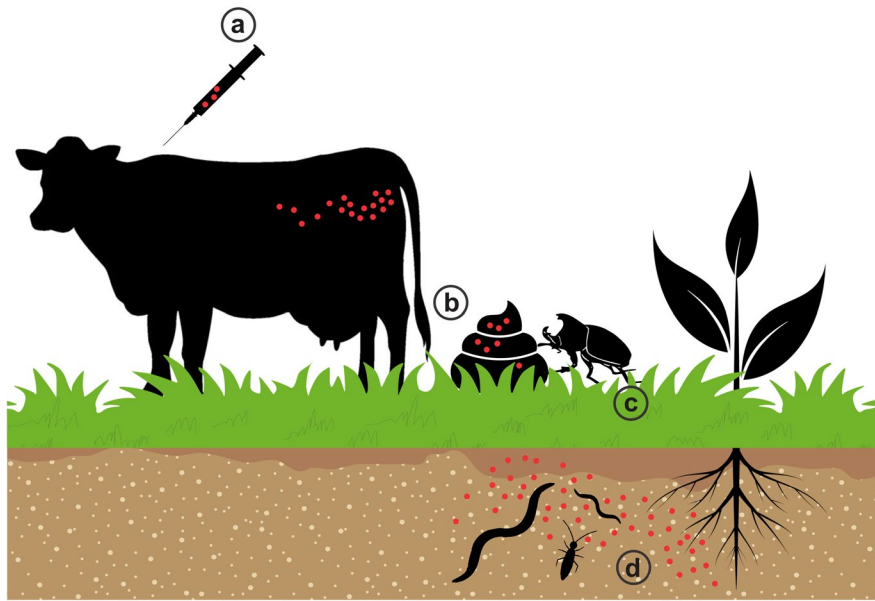


Fig. 1 Overview figure indicating the main pathway of avermectins to soil. **A.** The main method avermectins enter the environment occurs through their administration in livestock; **B.** 98% of the administered dose of avermectins can be excreted as a non-metabolized drug via feces. **C.** Beetles

are the major manure decomposer and, consequently, can be directly affected by contaminated dung. **D.** When the dung is decomposed, avermectins are released to the soil and can be absorbed by plants and soil invertebrates, such as earthworms, springtails and enchytraeids; Red dots represent avermectins

presence of a double bond between C22 and C23, or the presence of hydrogen at C22 and a hydroxy group at C23, respectively. Variants “a” have secbutyl in C25, while variants “b” have isopropyl (Vercruyssen & Rew, 2002). These differences in chemical conformation are responsible for altering the bioactivity of the molecule, demonstrating greater or lesser effectiveness in controlling parasites.

Initial tests showed that the four AVMs (A1, A2, B1, and B2) showed some efficiency in treating sheep parasites, but series B AVMs were the most reactive. Within the “B” AVMs, differences in toxic activity were also observed, and when administered orally, AVM B1 was more active than B2. Moreover, when administered parenterally, AVM B2 was more efficient. Thus, the pharmaceutical industry focused on commercially developing products based on the “B” series (Campbell et al., 1983).

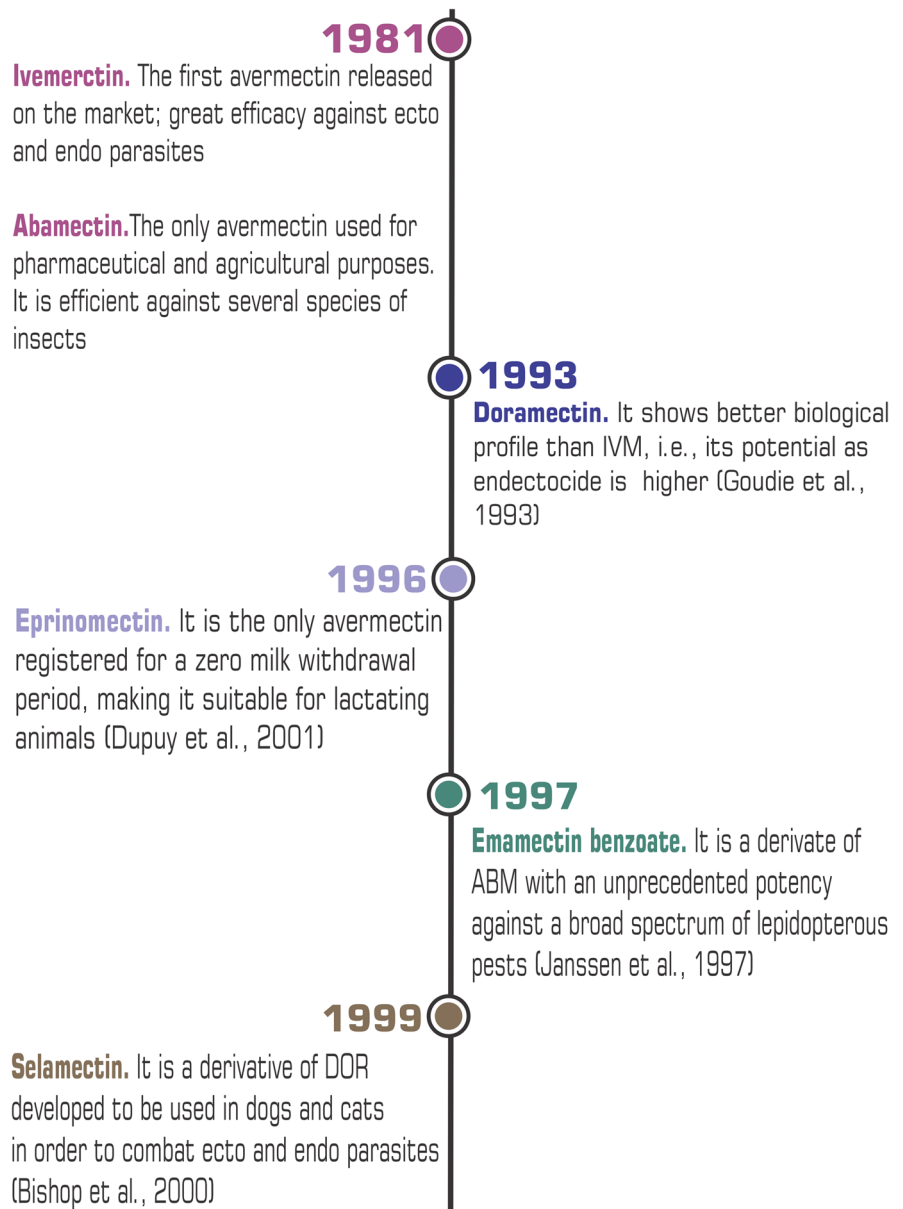
Although the AVM family is composed of different molecules that have been developed over the years for different uses (Fig. 2), the best known are ivermectin (IVM) and abamectin (ABM). Since the 2000s, doramectin (DRM), selamectin, eprinomectin, and emamectin benzoate have been used with

excellent results at low doses (Danaher et al., 2006; Giannetti et al., 2011) (Table 1). According to Turner and Schaeffer (1989), all family members have a similar mode of action, with small qualitative differences. The mechanism of action is related to the chlorine channels, present throughout the nervous system of invertebrates and vertebrates and mediated by different neurotransmitters.

2.1 Ivermectin (IVM)

In 1981, ivermectin (Fig. 3A) became the first commercially available avermectin-containing product on the market (Campbell, 1985; Chabala et al., 1980). IVM consists of a mixture of at least 80% 22,23-dihydro-avermectin B1a, and not more than 20% of the corresponding b homologue (22,23-dihydro-avermectin B1b) (Campbell, 1985) with broad spectrum against nematodes (Shoop et al., 1995). Its effectiveness, safety margin, and new mode of action quickly made it favorable for combating nematodes and arthropods in cattle, sheep, pigs, and horses (Campbell et al., 1983).

Fig. 2 Development of avermectins drugs over the years



Nowadays, IVM is available in many forms for large and small animal applications. However, recent data shows evidence that continued use of IVM over 40 years to control gastrointestinal parasites has caused drug resistance in some animals (Geurden et al., 2015; Macrelli et al., 2019; Waghorn et al., 2016).

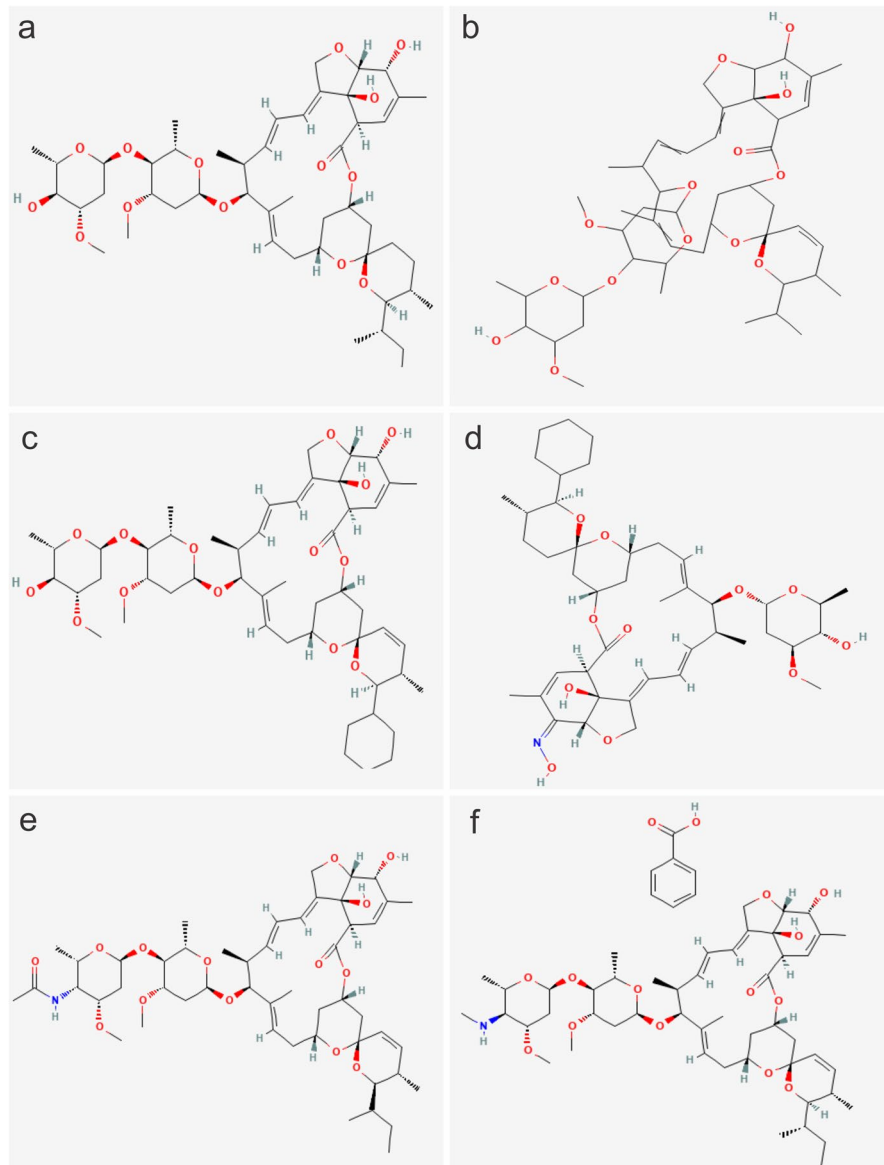
In humans, it is approved for the treatment of strongyloidiasis and onchocerciasis (Merola and Eubig, 2012). Recently, research has been successfully conducted examining its antiviral activity against a broad range of viruses, including dengue

(Tay et al., 2013), West Nile Virus (Yang et al., 2020), Venezuelan equine encephalitis virus (Lundberg et al., 2013), influenza (Götz et al., 2016), and SARS-CoV-2 (Caly et al., 2020). In these cases, ivermectin has been shown to inhibit nuclear import of host and viral proteins, probably due to how many different RNA viruses rely on IMP α / β 1, a protein responsible for nuclear import, during infection (Caly et al., 2012; Jans et al., 2019). Regarding SARS-CoV-2 (COVID-19), it is important to note that the experiment was conducted only in vitro using a dosage not

Table 1 Characteristics of different types of avermectins

Avermectin	Molecular formula	Uses	Release in the market
Ivermectin	$C_{48}H_{74}O_{14}$	Against nematodes and arthropods in cattle, sheep, pigs, and horses. In humans, for the treatment of strongyloidiasis and onchocerciasis	1981
Abamectin	$C_{95}H_{142}O_{28}$	Pharmaceutical and agricultural purposes	1985
Doramectin	$C_{50}H_{74}O_{14}$	It has a better biological profile compared to IVM to combat nematodes and arthropods	1993
Selamectin	$C_{43}H_{63}NO_{11}$	Control both endo- and ectoparasites in dogs and cats	1999
Eprinomectin	$C_{50}H_{75}NO_{14}$	Administered to animals in the lactation phase to combat parasites	1996
Emamectin benzoate	$C_{56}H_{81}NO_{15}$	Control of lepidopterous pests	1997

Fig. 3 Chemical structure of avermectins. **A.** ivermectin; **B.** abamectin; **C.** doramectin; **D.** selamectin; **E.** eprinomectin; **F.** emamectin benzoate. Source: <https://pubchem.ncbi.nlm.nih.gov/>



recommended for humans (Chaccour et al., 2020). Also, some initiatives are working to establish the addition of IVM as a vector control to interrupt malaria transmission (Molento, 2020).

2.2 Abamectin (ABM)

Of the AVM family, abamectin (Fig. 3B) (> 90% B1a and < 10% B1b) is the only one used for pharmaceutical and agricultural purposes (Shoop et al., 1995). It differs from IVM by the absence of a methylene group in position 26 (Campbell, 2012). During initial testing, only ABM showed positive results in controlling a wide range of insects, including members of the orders Diptera, Homoptera, and Coleoptera. Thus, ABM was selected for the control of pests of economic importance in agriculture (Dybas, 1989).

It is considered highly toxic by the US Environmental Protection Agency, but its popularity has grown due to its high efficacy, especially for termites (Bai & Ogbourne, 2016).

2.3 Doramectin (DRM)

Doramectin (Fig. 3C) (25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl) AVM A1a) is produced through a technique called mutational biosynthesis, which is used to prepare AVMs modified at the C-25 position by fermentation of a mutant *S. avermectinius* strain (Dutton et al., 1991). Structurally, DRM is more similar to ABM than to IVM (Prichard et al., 2012). After a number of biological and pharmacokinetic tests, DRM presented a better biological profile compared to IVM (Goudie et al., 1993).

2.4 Selamectin (SLM)

Selamectin (Fig. 3D), (25-cyclohexyl-25-de(1-methylpropyl)-5-deoxy-22,23-dihydro-5-(hydroxylimino) avermectin B1 monosaccharide), a doramectin-derived AVM, was the first AVM developed with the purpose to control both endo- and ectoparasites in dogs and cats (Bishop et al., 2000). It has been marketed since 1999 for the treatment and prevention of fleas and heartworms and in the treatment of *Otodectes cynotis*, *Toxocara cati*, and *Ancylostoma tubaeforme*. If administered

with sarolaner, it may also control ticks (Otranto & Little, 2017).

2.5 Eprinomectin (EPM)

The residues of AVM found in milk have always been a concern regarding the administration of these drugs in livestock (Giannetti et al., 2011). Thus, Shoop et al. (1996) developed a novel AVM-derivative, called eprinomectin (Fig. 3E) (4"-epi-acetyl-amino-4"-deoxy-avermectin B1). It has a reduced risk to humans since much lower amounts of residues turn up in milk, compared to other AVMs (Dupuy et al., 2001). It can also be administered to animals in the lactation phase (Baoliang et al., 2006).

2.6 Emamectin Benzoate (EMB)

Although ABM is effective against termites and various other insects, it is less effective against most species of the order Lepidoptera. This spectrum deficiency prompted a testing program that resulted in the discovery of emamectin (Fig. 3F) (4"-epi-methyl-amino-4"-deoxy-avermectin B1) in 1984, which was derived from ABM via a five-step synthesis. Adding benzoate salt to the molecule, thermal stability was improved and water solubility was increased (Jansson et al., 1997).

3 Ecotoxicological Effects

From an environmental point of view, the AVMs used in agriculture, such as ABM, and in livestock, such as IVM and EPM, are the ones that generate major concern due to the large amounts of both substances being released into the environment. In addition, their physicochemical characteristics (low volatility, low water solubility, high affinity for lipids and organic matter) combined with the high excretion rate of the compounds without undergoing metabolism raise concerns that toxic levels are being released into and are persisting in the environment (Kovecses & Marcogliese, 2005).

AVMs reach the environment mainly through feces after administration to cattle, sheep, and horses. According to Campbell et al. (1983), 98% of the administered dose of AVM is released by the feces without undergoing any metabolism process; Chiu et al. (1990) observed that in cattle, sheep, and rats over 90% of the active ingredient of IVM can be released by feces and less than

2% by urine. However, it is important to note that factors such as route of administration, dose, animal species, and pharmaceutical formulation influence the concentration of AVM excreted in feces (Chiu et al., 1990; Cook et al., 1996; Lifschitz et al., 2007). Several studies have already been conducted to analyze the pharmacokinetics and excretion of AVMs. According to Fernández et al. (2009), in cattle, the maximum IVM concentration found in feces after a single subcutaneous application of 2 mg/kg was 0.87 µg/g 134 h after application. In sheep, the same dose and route of application showed a maximum concentration of 0.93 µg/g 46 h after application. Even 17 days after application, IVM could still be detected in feces (Vokřál et al., 2019). AVMs can also enter the environment indirectly by applying manure to the soil (Boxall et al., 2002; Subbanna et al., 2020).

When released into the environment, various aspects, such as the physicochemical properties of molecules, soil structure, climatic conditions, and vegetation and fauna characteristics, can influence their impacts (Iglesias et al., 2018). In temperate climates, excreted ivermectin can remain active for up to two months in pastures (Madsen et al., 1990), while in Mediterranean climates, it was not detected in feces after 6 days (Lumaret et al., 1993).

The ecotoxicity of AVM to soil invertebrates is closely related to its mode of action. AVMs generally work by allowing more chloride ions to enter the cells, causing hyperpolarization and culminating in paralysis of the invertebrate neuromuscular systems. At the cellular level, AVMs prevent the transmission of electrical impulses in the muscles and nerves by amplifying the glutamate effects on the invertebrates-specific gated chloride channel (GluCl) (Bloomquist, 2003; Subbanna et al., 2020). In addition to GluCl effects, AVM also acts as an antagonist to 4-aminobutyric gamma (GABA), a neurotransmitter also present in muscle cells. The chloride ion flux produced by the opening of the channel into neurons results in loss of cell function and disruption of nerve impulses (Reddy, 2012). Thus, the action of AVM in the organism is to inhibit the movements (Abongwa et al., 2017). Once the organism is paralyzed, activities such as feeding and reproduction are interrupted resulting to starvation, decreasing of cocoon production and ultimately death. Adverse effects of AVM to mammals are not observed due to the lack of glutamate-gated chloride channels, the low affinity of AVMs for other mammalian ligand-gated chloride channels and

their inability to readily cross the blood–brain barrier (Arena et al., 1995).

Studies on the possible environmental impacts of AVMs have been carried out mainly for soil, since they have low solubility in water and are not expected to be present in this environmental compartment; however, biological effects on aquatic fauna have also been recorded (Ghais et al., 2019; Mesa et al., 2017). In soil, most studies focus on biological effects such as the mortality rate of insects that inhabit and feed on animal feces. There are fewer studies of their effects on plants, as it was believed that AVMs could not be absorbed by them (Halley, Nessel, et al., 1989).

3.1 Effects on Plants

Plants are considered excellent bioindicators for the detection of toxic substances in the soil, since they have characteristics that allow the evaluation of various parameters, such as germination, growth, and alterations in genetic material. Additionally, they play an important role in the food chain, are easy to handle and maintain in the laboratory, are inexpensive, and pose no ethical conflicts. Studies have also shown that results with plants are similar to animal tests, and in some cases the plants can be more sensitive (Minissi & Lombi, 1997; Wang & Freemark, 1995).

Early tests involving the effects of AVMs on plants revealed that the leaves were not able to absorb these drugs. According to Bull et al. (1984), IVM is rapidly degraded in cotton leaves, probably through photodegradation, and 8 days after application, only 1.4% of the IVM was found inside the leaf. Similar data were obtained by Bloom and Matheson (1993) in a study conducted by the Food and Drug Administration (FDA) where 17 plant species were exposed to high rates of different IVM analogs. The authors concluded that the substance was not absorbed by plants from the soil or when sprayed directly onto the leaves. The same results were obtained by Moye et al. (1987) in soybean, carrot, lettuce, and turnip crops exposed to ABM. Green et al. (1985) reported mild symptoms of phytotoxicity in ferns and slight spotting of carnation foliage when the indicated dose of ABM was followed, while Putter et al. (1981) concluded that AVM B2a was not phytotoxic to tomatoes and squash.

Thus, the absence of phytotoxicity reported in these studies was related to the non-absorption of AVMs by plants, which also explains the reduced number of studies related to the toxic effects of AVMs on these organisms. To the best of our knowledge,

there are no phytotoxicity studies for DRM, EPM, and EMB.

However, recent discoveries contradict what was previously considered the consensus. Moxidectin, an anti-parasitic substance also closely related to AVMs, as they belong to the macrocyclic lactone family, can negatively affect plant species in temperate grasslands (Eichberg et al., 2016). In the study, sheep feces containing moxidectin significantly reduced the germination of *Centaurea acea*, *Galium verum*, and *Plantago lanceolata* species, and the commercial formulation (Cydectin) showed more phytotoxic action.

Regarding AVMs, Iglesias et al. (2018) reported high concentrations of IVM in plants growing close to the experimental dung pats, suggesting that IVM moves from feces to both underlying soil and neighboring plants. Once absorbed by the plant, several biological effects can be observed. Vokřál et al. (2019) reported a significant decrease in *Sinapis alba* root growth in the presence of IVM at 50 and 500 nM concentrations, although germination had not been affected. The lowest concentration inhibited growth by 20% and the highest concentration inhibited growth by 24%.

The mixture of ABM + emamectin benzoate was not able to change the germination rate of *Allium cepa* (onion), but root growth was reduced by the highest concentrations tested (0.6 to 1.0 mL/L) (Ahmed, 2014). According to Macar (2021), all concentrations of ABM (0.025 mL/L, 0.050 mL/L, and 0.100 mL/L) were capable of inducing dose-dependent changes in parameters such as growth level, micronuclei abundance, chromosomal aberrations, and oxidative stress in *A. cepa*. The commercial formula of ABM, known as Kraft 36 EC®, presented severe toxicity to *A. cepa* and *Lycopersicon esculentum* (tomato) at the recommended dose and the specie *A. cepa* was more sensitive to the drug than the specie *L. esculentum* (Figueirêdo et al., 2020).

Although the number of studies performed on plants have been even scarcer than studies dealing with other organisms, evidence based on recent studies suggests that AVM may negatively affect plants. In addition, Bártíková et al. (2016) point out that the fact that the toxicity of drugs has not been studied does not mean toxic and adverse impacts on the environment do not exist. Moreover, a better understanding of the phytotoxicity caused by AVM may help in the development of bioremediation strategies for

contaminated areas. It is also worth noting that plants might be extremely sensitive to certain substances and may indicate levels of contamination in a given area, preventing the loss of biodiversity.

3.2 Effects on Soil Invertebrates

When released into the environment, soil is the first and main compartment reached by AVMs, either by direct application as a pesticide in crops, by the release in the feces and urine of livestock, or by accident. Therefore, different groups of soil-dwelling invertebrates are exposed to AVMs, which may cause biological effects leading to a decreased biodiversity of the area. Among the AVMs, IVM, ABM, and EPM are the drugs we can consider harmful to soil. Regarding ecotoxicological effects, IVM is the best known, while the ecotoxicity of ABM, EPM, and DRM is not properly understood yet.

3.2.1 Toxicity to Dung Beetles

The first studies on the adverse effects of AVM on feces were performed with flies and showed a decrease in the emergence of the species, a satisfactory result since these organisms are considered pests (Miller et al., 1981; Schmidt, 1983). However, it would be naive to assume that only pests would be affected by the drug (Strong & Brown, 1987). Thus, the first results regarding the toxicity in non-target organisms were published in the 1980s and showed a decrease in the number of beetle individuals in IVM-contaminated feces (Madsen et al., 1990; Wall & Strong, 1987). According to Wardhaugh and Rodriguez-Menendez (1988), a single injection of calves with IVM at the recommended dose rate of 200 µg/kg of body weight can cause a 90% mortality rate in beetles (*Copris hispanus*) in dung on days 2 and 3 after application and a 27.5% mortality rate in dung on day 16.

Since the 1990s, more attention has been given to the adverse effects of AVM, especially on the toxicity to beetle species. Beetles (Scarabaeidae: Scarabaeinae) are the major manure decomposer in both temperate and tropical agriculture (Slade et al., 2016), with more than 100 species being attracted to a single dung pile (Dacke & Jundi, 2018). In addition to contributing to soil fertility through decomposition (Nichols et al., 2008), it has recently been found that they are also important in reducing carbon dioxide

emission from pastures (Iwasa et al., 2015; Penttilä et al., 2013; Slade et al., 2016).

The behavior (attraction/repulsion) of dung beetles exposed to AVM has been contradictory, but the progress in the studies on the toxicity of AVM to non-target organisms might explain satisfactorily the results previously found. Until recently, some authors considered that beetles were attracted to the contaminated dung (Wardhaugh & Mahon, 1991; Holter et al., 1993a; Floate, 1998, 2007; Errouissi and Lumaret, 2010) while other authors thought that the contaminated dung has a “repelling” action (Floate, 2007; Holter et al., 1993b; Webb et al., 2010). Thus, the authors considered that the attraction/repulsion responses are probably due to an unpredictable side effect (Holter et al., 1993a) or to differences in cattle feed (Barth, 1993; Floate, 1998). Wratten and Forbes (1995) suggested that AVM treatment can decrease dung humidity and thus attracts fewer beetles; Wardhaugh and Mahon (1991) and Lumaret et al. (1993) suggested that the application of AVM alters the intestinal flora and, consequently, the quality of the feces.

However, the attraction response observed in some studies seems to be more related to the mode of action of AVM in cells. As the action of AVM in the organism is to inhibit the movements (Abongwa et al., 2017), the possible attraction demonstrated by AVM may actually be a reflection of the entrapment of organisms in contaminated feces: once present in the contaminated site, AVM act on the neurotransmitters and the ability to produce movements is shut down, so the animals are not able to move to an uncontaminated site. According to Verdú et al. (2015), IVM can decrease both the locomotor and olfactory capacities of the *Scarabaeus cicatricosus* beetle, preventing them from performing basic biological functions.

As can be seen in Table 2, a great number of studies conducted over the past 30 years on the adverse effects of AVMs can be found in the scientific literature. These studies were performed mainly using IVM, but some studies using ABM (Dadour et al., 2000; Wardhaugh & Mahon, 1991; Webb et al., 2010) and EPM (Ishikawa & Iwasa, 2019a; Iwasa & Sugitani, 2014; Wardhaugh, Holter, et al., 2001) can be found as well. Analyzing the effects demonstrated by AVMs on dung beetles it is possible to affirm that several biological parameters, such as survival, reproduction, and larvae development, can be affected. Among the studies shown in Table 2, only

the one conducted by Kryger et al. (2005) observed no negative effects on dung beetles, and species’ richness and diversity were not affected by the presence of IVM. However, the authors point out that weather conditions, among other factors, may have affected the result, since the experiment was conducted under a high-rainfall condition.

Because climate conditions are an important factor when evaluating the ecotoxicity, studies conducted in different world regions, including tropical, sub-tropical, and temperate climates, are essential. Moreover, species from tropical regions differ from species from temperate regions in their reproductive and feeding habits and may present different responses to AVMs. However, studies suggest that organisms from both regions have similar responses to AVMs. In tropical and sub-tropical regions, authors have observed larval mortality (Pérez-Cogollo et al., 2017; Sommer & Nielsen, 1992), adult mortality (Dadour et al., 2000; Wardhaugh, Holter, et al., 2001; Wardhaugh, Longstaff, et al., 2001), and attraction response (Holter et al., 1993a, 1993b; Rodríguez-Vivas et al., 2019). In temperate regions, similar effects have been observed (Fincher, 1992; Errouissi et al., 2001; O’Hea et al., 2010; Iwasa & Sugitani, 2014; Ishikawa & Iwasa, 2019a, 2019b; Weaving et al., 2019).

Mortality is considered a lethal response, but sublethal responses may indicate that the ecosystem services dung beetles provide may be more severely compromised than indicated by the understanding of the lethal effects (Manning et al., 2017). Given this knowledge, some studies have focused on cellular effects, mainly related to reproduction. ABM and DRM may limit oocyte development by reducing their quantity and size (Dadour et al., 2000; Houlding et al., 1991). In male beetles, IVM may alter the size of the follicles of the testes (Cruz-Rosales et al., 2012). Recently, Martínez et al. (2017) and Weaving et al. (2019) observed that IVM can alter ovarian morphology by stopping vitellogenesis and reducing oocyte size. Thus, the combined lethal and sublethal effects in dung-beetles are likely to reduce the abundance of these non-target organisms on farms that use AVM treatment, especially those that have used it for longer periods.

3.2.2 Toxicity to Other Non-target Soil Invertebrates

In order to completely evaluate the risks of a determined substance in the environment, it is necessary to

Table 2 Effects of avermectins on dung-beetle species after exposure to contaminated dung

Test organism	Avermectin	Dose rate/animal	Effects	Reference
<i>Onthophagus binodis</i>	Abamectin	0.2 mg kg ⁻¹ /cattle	Adult survival was not affected; oviposition was reduced and immature survival was zero in dung from animals treated one week previously, returning to normal 8 weeks after treatment	Ridsdill-Smith, 1988
<i>Copris hispanus</i>	Ivermectin	0.2 mg kg ⁻¹ /cattle	90% mortality in dung dropped on days two and three after injection and 27.5% mortality in dung of day 16; feeding activity was suppressed in dung of days 1–8; oviposition rate was reduced and immature survival was zero when fed with day 3 dung	Wardhaugh & Rodriguez-Mendez, 1988
<i>Bubas bubalus</i>			No mortality among sexually mature adults when fed for five weeks on dung collected at intervals ranging from 1–32 days after injection	
<i>Onitis belial</i>			Substantial mortality was recorded among newly emerged beetles	
<i>Aphodius spp</i>	Ivermectin	0.2 mg kg ⁻¹ /cattle	Larvae were inhibited in dung from animals treated 1 day previously	Madsen et al., 1990
-	Abamectin	0.2 mg kg ⁻¹ /cattle	Five species of dung beetle were significantly attracted by the contaminated dung compared to untreated dung	Wardhaugh & Mahon, 1991
		0.2 mg kg ⁻¹ /sheep	Contaminated dung attracted a significantly higher proportion of beetles (<i>O. australis</i>)	
<i>Euoniticeilus fubus</i>	Ivermectin	0.2 mg kg ⁻¹ /cattle	Inhibited development	Lumaret et al., 1993
-	Ivermectin	0.2 mg kg ⁻¹ /cattle	In one Danish trial, beetles preferred control dung and no preference was found in two other experiments; in Tanzania, the tendency was to prefer control dung; in Zimbabwe, two species preferred dung from treated cattle, whereas three others did not discriminate between dungs	Holter et al., 1993b

Table 2 (continued)

Test organism	Avermectin	Dose rate/animal	Effects	Reference
<i>Onthophagus gazella</i>	Ivermectin	0.2 mg kg ⁻¹ /cattle	Dung collected 2 and 7 days after treatment was lethal to newly hatched larvae; normal head capsule development was inhibited	Sommer and Nielsen, 1992
<i>Aphodius spp</i>	Ivermectin	0.2 mg kg ⁻¹ /cattle	No significant differences in the number of adult found in the dung; the development of larvae for at least 7 days after treatment were prevented	Strong & Wall, 1994
<i>Euoniticellus intermedius</i> <i>Onthophagus gazella</i>	Ivermectin	0.2 mg kg ⁻¹ /cattle and 0.02 mg kg ⁻¹ /cattle	The two treatment levels had no effect on the production of brood balls by either species of dung beetle; emergence of adult from brood balls made with dung from cattle that received the 0.2 mg kg ⁻¹ dose was reduced for 1 and 2 weeks for both species	Fincher, 1992
<i>Euoniticellus intermedius</i>	Ivermectin	0.2 mg kg ⁻¹ /cattle	Reduced adult emergence from dung collected 2–7 days after treatment; specimens that developed in dung collected 1 and 14 days after treatment were less productive in their first breeding	Krüger & Scholtz, 1997
<i>Omitis alexis</i>			Adult emergence was reduced between 2 and 7 days after treatment	
<i>Onthophagus binodis</i>	Abamectin	0.2 mg kg ⁻¹ /cattle	Fewer emerged adults of <i>O. binodis</i> survived exposure to dung from cattle treated 3 and 6 d previously with abamectin or 9 d previously with doramectin; both compounds induced a range of sublethal effects	Dadour et al., 2000
<i>Onthophagus taurus</i>	Eprinomectin	0.5 mg kg ⁻¹ /cattle	High juvenile mortality during the first 1–2 weeks after treatment; increased mortality among newly emerged beetles fed on feces collected 3 days after eprinomectin treatment	Wardhaugh, Holter, et al., 2001
-	Ivermectin	0.2 mg kg ⁻¹ /cattle	There was no observable effect on the dung beetle communities	Kryger et al., 2005
<i>Aphodius constans</i>	Ivermectin	Slow-release bolus (12 mg·day ⁻¹ over 135 days)	Negative effects on the development of larvae, even at a low concentration	Errouissi et al., 2001

Table 2 (continued)

Test organism	Avermectin	Dose rate/animal	Effects	Reference
<i>Onthophagus taurus</i> <i>Euoniitellus fubvus</i>	Ivermectin	controlled-release capsules/sheep	Almost no beetle larvae survived after 39 days; newly emerged <i>O. taurus</i> suffered significant mortality whereas those that survived underwent delayed sexual maturation; there was no effect on the survival of sexually mature beetles, but reduced the fecundity of <i>O. taurus</i>	Wardhaugh, Longstaff, et al., 2001
<i>Aphodius spp</i>	Abamectin	0.5 mg kg ⁻¹ /cattle	Beetles preferentially colonized dung of untreated cattle	Webb et al., 2010
-	Ivermectin	Slow-release bolus (12 mg·day ⁻¹ over 135 days) 0.2 mg kg ⁻¹ /cattle	Significant attractive effect	Errouissi & Lumaret, 2010
<i>Aphodius ater</i> <i>Aphodius rufipes</i>	Ivermectin		Larval development rates were significantly reduced; significant negative effects on the survival of larvae	O'Hea et al., 2010
<i>Caccobius jessoensis</i>	Eprinomectin	0.5 mg kg ⁻¹ /cattle	No significant differences in the numbers of brood balls; adult emergence rates were significantly reduced on days 1 and 3 post-treatment	Iwasa & Sugitani, 2014
<i>Liatongus minutus</i>			Lab. Experiment: No significant differences in the numbers of brood, but survival rates of larvae were significantly reduced on days 1 and 3 post-treatment. Field experiment: the numbers of brood balls were significantly larger in number in dung from treated cattle; survival rates of larvae in these brood balls were significantly reduced 1 day post-treatment in dung pats from treated cattle	

Table 2 (continued)

Test organism	Avermectin	Dose rate/animal	Effects	Reference
<i>Onthophagus landolti</i>	Ivermectin	0.2 mg kg ⁻¹ /cattle	Adult survival was not affected; suppressed fecundity of beetles at 3, 6 and 14 days post-treatment (dPT) and reduced fecundity at 28 dPT; larval survival was significantly reduced only at 3 dPT	Pérez-Cogollo et al., 2017
		0.63 mg kg ⁻¹ /cattle	Adult survival was not affected; suppressed fecundity of beetles at 3, 6, 14 and 28 dPT, and reduced fecundity at 35 dPT; significantly reduced larval survival at 6, 14 and 28 dPT	
<i>Onthophagus lenzii</i>	Eprinomectin	0.5 mg kg ⁻¹ /cattle	Adult survivals, numbers of brood balls constructed and adult emergence rates were significantly reduced	Ishikawa & Iwasa, 2019a
<i>Copris ochus</i>			Adult survivals were significantly reduced; numbers of brood balls were significantly reduced in dung at 7 days; adult emergence rates were not affected	
<i>Copris acutidens</i>	Ivermectin	0.5 mg kg ⁻¹ /cattle	Adult survivals, numbers of brood balls and adult emergence rates were significantly reduced	Ishikawa & Iwasa, 2019b
<i>Onthophagus bivertex</i>			No effects on adult survival or feeding activities; numbers of brood balls and adult emergence rates were significantly reduced	
<i>Onthophagus lenzii</i>			No effects on adult survival or feeding activities; adult emergence rates were significantly reduced	
<i>Pheilotrupes auratus</i>			No effects observed	
<i>Onthophagus landolti</i>	Ivermectin	0.2 mg kg ⁻¹ /cattle	Feces of IVM-treated cattle attracted more individuals than IVM-free feces	Rodríguez-Vivas et al., 2019

Table 2 (continued)

Test organism	Avermectin	Dose rate/animal	Effects	Reference
<i>Sisypus rubrus</i>	Dectomax® (doramectin)	1 mL per 10 kg body weight	Larvae were smaller than larvae initially laid in control dung; significantly greater proportions of dead larvae	Mackenzie et al., 2021
	Endomec® (abamectin)	1 mL per 20 kg body weight	Larvae were smaller than larvae initially laid in control dung; significantly greater proportions of dead larvae	
<i>Onthophagus binodis</i>	Dectomax® (doramectin)	1 mL per 10 kg body weight	Larvae had significantly lower masses and head capsule widths than those in control groups; significantly greater proportions of dead larvae	Mackenzie et al., 2021
	Endomec® (abamectin)	1 mL per 20 kg body weight	Significantly lower mass than control larvae; significantly greater proportions of dead larvae	
<i>Onitis viridulus</i>	Dectomax® (doramectin)	1 mL per 10 kg body weight	Larvae had smaller masses and head capsule widths; significantly greater proportions of dead larvae	Mackenzie et al., 2021
	Endomec® (abamectin)	1 mL per 20 kg body weight	Larvae had smaller masses and head capsule widths; significantly greater proportions of dead larvae	

use the largest number of non-target species as possible. Since AVM toxicity in dung-beetles is well established, researchers are now focused on understanding its toxicity on other species inhabiting the soil. Earthworms (Anelida), springtails (Collembola), and enchytraeids (Anelida) are considered good bioindicator organisms to evaluate soil toxicity due to their representativeness to soil fauna (ISO, 16387, 2012; ISO 11268–2, 2015; ISO, 11267, 2019). For this reason, this topic focuses on the effects of AVMs in these species. Only studies conducted on soil or dung-soil association, under laboratory or field conditions, have been considered.

The first report in the scientific literature regarding AVM toxicity in earthworms was conducted by Halley, Jacob, et al. (1989). According to the authors, IVM has no significant adverse effects to earthworms, even dung inhabitants, due to its low dose in the environment. During the 90 s, similar results were found by the few studies conducted to analyze IVM toxicity on earthworms. Wang et al. (1990) suggested low toxicity for the species *Eisenia fetida* when exposed to artificial soil and filter-paper contaminated with IVM, ABM, and emamectin benzoate; Madsen et al. (1990) observed no adverse effects in earthworms exposed to IVM-contaminated dung, as the number of individuals and biomass loss were non-significant. Regarding enchytraeid and springtails species, no studies in the 1990s were conducted to evaluate the negative effects of AVMs. In the early 2000s, studies suggested that AVMs were not toxic to earthworms (Halley et al., 2005; Sun et al., 2005a, 2005b; Svendsen et al., 2003, 2005). According to them, AVMs cannot affect mortality, behavior, growth, biomass, or number of individual of earthworms in contact with AVMs.

Recently, concerns regarding AVM soil toxicity grew after some studies suggested that the environmental effects caused by AVMs could be greater than previously reported. Jensen et al. (2007) observed significant toxicity of ABM on the growth of *E. fetida* with increasing concentrations up to 5 mg/kg where cocoon production and hatchability were the most sensitive parameters. To the earthworm *Perionyx excavatus*, cocoon production was significantly reduced in the presence of ABM and no cocoons were produced at doses of 20 mg/kg or higher, while ABM at 50 mg/kg induced extreme pathology, characterized by the loss of the integrity of the whole body wall and intestine (Ng et al., 2019). Diao et al. (2007)

also observed a significant effect on the reproduction of *E. fetida* caused by ABM, but no change in the survival or juvenile growth was observed. Goodenough et al. (2019) and Nunes et al. (2016) also reported no effect on the survival of earthworms exposed to IVM and ABM, respectively. On the contrary, according to Bang et al. (2007), IVM can increase the mortality of *E. fetida*, reaching a 98.3% mortality rate in dung excreted 2 days after dosing, and it can also change growth rates, since the growth rate was 75% lower than that recorded for the control worms fed dung 1 day after drug application.

Mortality, a lethal effect, seems to be the least sensitive parameter when earthworms are exposed to AVM. However, sublethal effects should be considered when assessing the toxicity of the substances. In addition to altering reproduction rates, ABM can produce morphological alterations in *Eisenia andrei*, such as thinning, discoloration of the posterior region, constriction in different regions of the body, fragmentation, and loss of segments mainly in the posterior region (Nunes et al., 2016). Avoidance behavior has also been observed (Torkhani et al., 2011; Nunes and Espíndola, 2012).

The effects of AVMs on springtails (Collembola) and enchytraeids (Anelida) are not as well documented as earthworms; however, there is some information suggesting toxicity for these organisms. Several studies focused on assessing the lethal doses and effective concentration values, such as LD₅₀ (a concentration estimated to cause 50% mortality), EC₁₀, and EC₅₀ (concentrations estimated to cause 10% and 50% reduction in a determined parameter), as can be seen in Table 3. Additionally, values for NOEC (non-observed effect concentration) and LOEC (the lowest observed effect concentration) have also been determined.

These studies have been conducted on natural soils (Jensen et al., 2003; Goodenough et al., 2019; Jensen et al., 2009) and artificial soils (Figueirêdo et al., 2019; Kolar et al., 2008; Römbke et al., 2010; Zortéa et al., 2017) mainly in temperate conditions; there is scarce information regarding tropical conditions (Zortéa et al., 2017). Analyzing the data provided by EC₁₀, EC₅₀, and LD₅₀ experiments (Table 3), enchytraeids can be considered less sensitive to AVM. In a study conducted by Kolar et al. (2008) exposing soil invertebrates to DRM, LD values were > 300 kg⁻¹ of dry soil and > 2.5 kg⁻¹ of dry soil to enchytraeids

Table 3 Concentrations of avermectins causing negative effects on earthworms, springtails, and enchytraeids

Test organism	Avermectin	Substrate	EC ₁₀ (mg kg ⁻¹ dry soil)	EC ₅₀ (mg kg ⁻¹ dry soil)	LD ₅₀ (mg kg ⁻¹ dry soil)	NOEC	LOEC	Reference
<i>Folsomia fimetaria</i>	Ivermectin	sandy-loamy soil	0.26	1.7	8.4	0.3	-	Jensen et al., 2003
<i>Enchytraeus crypticus</i>			14.00	36	-	3	-	
<i>Folsomia fimetaria</i>	Abamectin	sandy-loamy soil	0.05	0.33	0.81	<0.25	0.25	Diao et al., 2007
<i>Folsomia candida</i>			0.19	0.68	>2.50	0.25	0.50	
<i>Enchytraeus crypticus</i>			12.7	23.7	-	10	25	
<i>Eisenia fetida</i>			0.06	0.39	>5.0	<0.25	0.25	
<i>Eisenia andrei</i>	Doramectin	Lufa 2.2 soil	-	-	228	8.4	-	Kolar et al., 2008
	Abamectin	Feces	-	>2.5	>2.5	2.5	-	
	Abamectin	Lufa 2.2 soil	-	-	18	9.8	-	
		Feces	-	>1.4	>1.4	>1.4	-	
<i>Folsomia candida</i>	Doramectin	Lufa 2.2 soil	26	42	>300	30	-	
		Feces	-	>2.5	>2.5	>2.5	-	
	Abamectin	Lufa 2.2 soil	5.2	13	67	1.5	-	
		Feces	-	>1.4	1.0	0.81	-	
<i>Enchytraeus crypticus</i>	Doramectin	Lufa 2.2 soil	79	170	>300	100	-	
		Feces	-	2.2	>2.5	<1.4	-	
	Abamectin	Lufa 2.2 soil	4.6	38	111	8.0	-	
		Feces	-	0.94	1.1	0.81	-	
<i>Eisenia fetida</i>	Ivermectin	OECD artificial soil	-	-	>10	2.5	-	Römbke et al., 2010
<i>Folsomia candida</i>			-	-	8.4	0.3	-	
<i>Folsomia fimetaria</i>	Ivermectin	Sandy clay loam soil	0.19	0.93	5.3	-	-	Jensen et al., 2009
<i>Enchytraeus crypticus</i>			14	36	>300	-	-	
<i>Folsomia candida</i>	Ivermectin	Tropical artificial soil	-	0.43	>10	<0.2	≤0.2	Zortéa et al., 2017
<i>Folsomia candida</i>	Abamectin	Lufa 2.2 soil	1.4	6.3	23	-	-	Figuerédo et al., 2019
<i>Eisenia fetida</i>	Abamectin	Artificial soil	-	-	9.68	-	-	Teng et al., 2021

EC10, EC50, NOEC (no-observed effect concentration) and LOEC (lowest observed effect concentration) refers to reproduction; LD50 refers to mortality; -:no data

and earthworms, respectively. According to the literature, the highest toxicity observed was caused by ABM on the springtail *F. fimetaria* in a sandy-loamy soil, since the EC_{10} and EC_{50} for reproduction and LD_{50} values were 0.05, 0.33, and 0.81 mg kg⁻¹ of dry soil, respectively; the NOEC value was also among the lowest observed (0.25 mg kg⁻¹ dry soil). In sandy-loamy soil, data also suggest that ABM is high toxic to earthworms (EC_{10} =0.06 mg kg⁻¹ of dry soil; EC_{50} =0.39 mg kg⁻¹ of dry soil) and that enchytraeids are less sensitive (EC_{10} =12.7 mg kg⁻¹ of dry soil; EC_{50} =23.7 mg kg⁻¹ of dry soil). The only study addressing the toxicity in tropical soil was conducted by Zortéa et al. (2017) and suggests IVM can be toxic to springtails (EC_{50} =0.43 mg kg⁻¹ of dry soil; LD_{50} > 10 mg kg⁻¹ of dry soil). The study was conducted in artificial soil, so studies in natural soils are needed to confirm these observations.

Regardless of values obtained for reproduction and survival and regardless of the experimental conditions, Diao et al. (2007), Jensen et al. (2009), and Römbke et al. (2010) concluded that AVMs are likely to pose a risk to soil-dwelling invertebrates under realistic exposure scenarios, although these studies should be complemented by the measurement or the prediction of the soil concentration of these compounds before the risk can be assessed more accurately (Jensen et al., 2003; Zortéa et al., 2017).

In a soil multi-species (SMS) higher tier test system, Jensen and Scott-Fordsmand (2012) introduced mutualism, competition, and predation within the system by adding five collembolan species, one enchytraeid species, and a predatory mite species in order to verify the toxicity of IVM. The authors observed that on the community level all treatments were significantly affecting the community abundance and composition and that a decrease in abundance corresponded with increasing concentrations of exposure for all species. However, in a field study comparing the abundance of earthworms and springtails in soil beneath dung from cattle that was either untreated or treated with IVM, Scheffczyk et al. (2016) observed little effect from the residues on either earthworms or springtails at the four study sites (The Netherlands, France, Canada, and Switzerland), given that the species' richness and abundance were not affected. However, the authors point out that significant effects observed at 3 sites suggest that springtail communities might be affected by IVM under

field conditions. In addition, no effects from IVM were detected under field conditions for springtails and earthworms by Römbke et al. (2010) and Svendsen et al. (2003), respectively.

4 Final Considerations

The use of AVMs to combat human and animal diseases is extremely necessary from a sanitary and economic point of view, and a Nobel Prize has even been awarded to researchers who made treatment with these drugs possible. However, from an environmental point of view, some doubts about its effects on non-target organisms, especially when used in livestock, arose after the 2000s.

AVMs were not believed to have any adverse effects on plants as they would not be able to absorb these drugs. Recent researches, however, suggest that plants are negatively affected and AVMs may cause phytotoxic effects such as reduced root germination and growth, and genotoxic effects such as chromosomal instability. Research on the effects of AVMs on plants is still scarce, but the recent findings should increase the interest of researchers to undertake more study in order to better understand the effects and mechanisms of its effect on plants.

On the other hand, there is ample information on the toxicity of AVMs in soil invertebrates, such as dung beetles, earthworms, springtails, and enchytraeids. This fact is expected since soil is the first and main compartment to be reached by AVMs. Moreover, dung beetles are closely related to feces, whereas earthworms, springtails, and enchytraeids are indicated as bioindicator organisms by international protocols such as ISO and OECD in the assessment of soil toxicity.

The data obtained from these studies strongly suggest that AVMs negatively affect soil invertebrates. In dung beetles, lethal effects, such as mortality, and sublethal effects, such as decreased reproduction, are observed. For other non-target organisms, mainly sublethal effects are observed. This is explained by the fact that the concentration of AVMs is higher in feces, which is inhabited by beetles. In soil, the concentration is lower, so the lethal effects are not always detected.

Since IVM is the first developed and most used AVM, the majority of the studies focused on its adverse effects, followed by ABM, the only AVM used as a pesticide in different crops. DRM and EPM, developed more

recently, are still not well studied regarding their environmental effects, while SLM and EMB are not considered an environmental concern because they are not widespread in the environment. However, the few studies on DRM and EPM also suggest environmental toxicity.

In the next years, the progress in the knowledge regarding the environmental effects of AVMs on non-target organisms must rely on certain approaches, such as (1) more plant species tested, (2) further studies focusing on ABM, DRM, and EPM effects, (3) soils from tropical regions must be included in the analyzes, (4) studies under field conditions must be performed to confirm results obtained in the laboratory (Scheffczyk et al., 2016), and (5) “omic” endpoints must be integrated with traditional bioassays as there is some evidence that pesticide-induced gene expression effects precede and occur at lower concentrations than organism-level responses (Figueirêdo et al., 2019).

According to the data available in the scientific literature shown here, the treatment of livestock with AVMs can negatively affect both plants and soil invertebrates. Thus, prudent and moderate use is recommended in order to reduce negative effects on non-target organisms.

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Declarations

Conflict of Interests The authors declare no competing interests.

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