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Mini Review

What do we know about the Effects of Pesticides on Helminths?

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Abstract

The term pesticides refer to compounds used to control pests and/or promote agricultural output. Although pesticides are formulated to be harmful only to one or a group of target organisms, this is often not achieved in practice. In recent years, the effect of agricultural activities on wildlife diseases has received much attention, especially those related to contaminants that affect host-pathogen interactions. This mini review focuses mainly on the effects of pesticides on helminths, summarizing the principal compounds that can influence the transmission or the biology of these parasites. The environmental changes caused by pesticides and consequent impact on host-parasite interactions are a major concern since they are implicated in the emergence or reemergence of various parasitic organisms in recent years. For example, it has been suggested that the amphibian population decline is closely linked to these environmental changes, especially because the pesticide exposure affects the host immunity, increasing the prevalence of trematode infection. The use of helminths under experimental conditions has been useful since it is possible to elucidate physiological, biological and morphological effects caused by pesticides. The biological effects on the larval stages of trematodes has received special attention since they require the aquatic environment to complete their life cycle and are thus more exposed to contaminants. Other research efforts have been directed at phytonematodes, to obtain alternative control/management chemicals that are less toxic to the environment than conventional ones. It is important to carry out studies to discover new strategies that minimize toxicity of the compounds currently used, focusing a more specific mechanism of action on the target organisms, and clarify the relevance on the helminths transmission

ABBREVIATIONS

EPA: Environmental Protection Agency; PAs: 1,2-dehydropyrrolizidine Alkaloids; POEA: Polyethoxylated tallow Amine; DDT: Dichlorodiphenyltrichloroethane

INTRODUCTION

The term pesticides refer to compounds used to control pests and/or promote agricultural output. Among the main classes are insecticides, herbicides, fungicides, molluscicides, rodenticides and nematicides. Organochlorine insecticides were successfully used to control a number of diseases, such as malaria, until the 1960s when they were banned due to harmful side effects, such as slow decomposition (high persistence), environmental degradation, low solubility in water, high solubility in hydrocarbon-sensitive media such as fatty tissues of living organisms, and high toxicity to insects and humans [1,2]. After that, from the 1960s to 1980s, organophosphate insecticides, carbamates and pyrethroids were introduced, as well as new herbicides and fungicides from 1970s onwards [1]. According to the U.S. Environmental Protection Agency (EPA), expenditures on herbicides are the largest portion of total expenditures on pesticides (40%), followed by insecticides, fungicides and other pesticides, respectively [3].

It is accepted that the use of pesticides increases production of food and reduces vector-borne diseases. However, serious health implications to humans and the environment also result from their use. The high groups at highest risk of exposure to pesticides are farm workers, especially those involved in formulating, mixing, loading and spraying pesticides. However, no segment of the population is completely protected against exposure to pesticides and the potentially serious health effects, particularly in developing countries. Estimates are that chronic diseases caused by exposure to pesticides affect about 1 million per year worldwide [4,5].

In addition to human health, these compounds contaminate the soil, water and vegetation and are toxic to many organisms, including birds, fish, beneficial insects and non-target plants [1]. In recent years, the effect of agricultural activities on wildlife diseases has received much attention, mainly those related to contaminants that affect host-pathogen interactions. These effects are also associated with modifications of potential physical interactions between hosts and pathogens, causing loss of biodiversity and affecting parasite transmission [6-8].

This mini review examines the effects of pesticides on helminths, focusing on the host-parasite interaction, particularly in the larval free-living stages of trematodes (miracidia and cercariae), and helminths used as experimental models and plant-parasitic nematodes to elucidate the effects on the biology of these parasites, summarizing the main compounds studied that can influence the transmission of these helminths (Figure 1).

The effects of pesticides on parasitism

Parasite transmission is strongly influenced by environmental changes, which can alter specific interactions of hosts, parasites, biotic and abiotic factors [9,10]. According to Bolker et al. [11], the factors that affect host and parasite ecology can be divided into those that are lethal and sublethal. While lethal factors reduce the density of hosts and/or parasites, sublethal factors alter the host immunity and/or parasite infectivity, consequently affecting the disease dynamics. These anthropogenic factors, such as the use of pesticides, can have concurrent positive and negative effects on parasite transmission, making it necessary to understand and quantify their net effects on disease emergence [10,12].

Net effects are the product of changes of survival and traits of both hosts and parasites, such as susceptibility and infectivity. Most research conducted to investigate host-parasite interaction related to pesticide exposure is focused on amphibians, because of their global decline [10,13,14]. Trematode infections of amphibians have received research attention because some species of trematodes are considered to be emerging parasites capable of causing limb deformities driven by anthropogenic environmental change [10,12,15-17]. Pesticides are among the factors that probably affect disease prevalence and intensity and are considered directly toxic to hosts and free-living stages of parasites, by altering their behavior and immunity, affecting parasite transmission and virulence [10,12,18-22].

The herbicide atrazine has been employed in different amphibian-trematode interaction studies with the purpose of evaluating its role as a driver of disease risk [10,12,23]. It is believed that atrazine increases the food source of gastropods (first intermediate host of trematodes), consequently increasing the abundance of trematode cercariae and the exposure of amphibians to infection [12,24]. Kiesecker [15] demonstrated in field and laboratory experiments that trematode infection explains the development of amphibian limb deformities. The exposure to pesticides, such as atrazine, malathion and esfenvalerate, in areas of agricultural runoff was found to decrease the host immunocompetency, resulting in higher parasite loads and limb deformities.

In an experimental study carried out by Rohn et al. [10], assessing the effect of two herbicides (the triazine herbicide atrazine and the glycine herbicide glyphosate) and two insecticides (the organophosphate insecticide malathion and the carbamate insecticide carbaryl) on six important mechanisms of host-parasite interaction (cercarial survival, tadpole survival, snail survival, snail growth and fecundity, cercarial infectivity, and tadpole susceptibility) using the trematode *Echinostoma trivolvis* and its first and second intermediate host, the snail *Planorbella trivolvis* and tadpoles of the green frog *Rana clamitans*, respectively. They observed that only atrazine significantly reduced cercarial survival at concentrations greater than found in aquatic ecosystems. No evidence was found that the pesticide treatments significantly affected the first intermediate snail host traits under the tested conditions. However, the sublethal exposure of *R. clamitans* to each of the four pesticides increased their susceptibility to infection, suggesting a negative impact of pesticides on second intermediate host immunity, increasing the infections caused by trematodes in amphibians, which could be one of the factors leading to their population decline.

The survival of parasites depends on successful transmission of infective stages to hosts. The free-living stages of trematodes (miracidia and cercariae), face challenges such as predation, the need to find suitable host and external environmental factors in their macrohabitats [25,26]. Abiotic factors (temperature, oxygen content and pH) and anthropogenic activities can influence the occurrence of parasites, affecting trematode infections since they are vulnerable to these factors. Several studies have been conducted of the influence of pollutants, especially heavy metals, on cercarial sensitivity [27-29]. Pesticides also have been shown

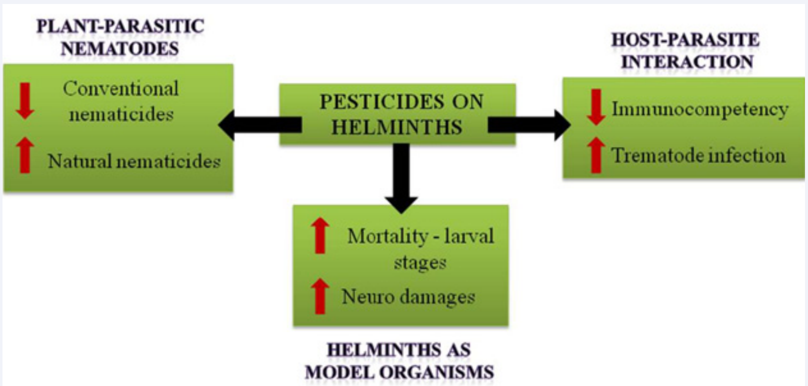

Figure 1 The main aspects of pesticides on helminths.

to have deleterious effects on miracidia and cercariae, as observed with molluscicides [30-32] and dichlorodiphenyltrichloroethane (DDT) insecticides [33].

Koprivnikar et al. [26], showed under experimental conditions the effects of atrazine on cercariae of four different trematode species: *Haematoloechus*, *Alaria*, *Megalodiscus* and *E. trivolvis*. The mortality and activity of cercariae varied among species and atrazine exposure was responsible for decreasing the ability of *E. trivolvis* to infect amphibians and the intensity of infection as well. More recently, Raffel et al. [34], found no evidence of biological effects when eggs and miracidia of *E. trivolvis* were exposed to the four pesticides cited above, including atrazine and glyphosate in high concentrations [10]. It is believed that cercariae are more sensitive than miracidia due to the longer exposure period to pesticides as a consequence of the longer life span and faster speed of contaminant uptake.

Effects of pesticides on helminths used as model organisms

Some helminth species have been used over the years as model organisms under experimental conditions for different purposes, such as *in vitro* and *in vivo* assays to screen potential commercial drugs with anthelmintic potential [35,36]. Among these are species of the genus *Echinostoma*, mainly *Echinostoma paraensei* and *Echinostoma caproni* [22,37-41]. Their adoption as a model stems in part from the fact that their life cycle is easy to reproduce under laboratory conditions, requiring low equipment and maintenance costs [42,43]. The most common research focus is about the biological effects of pesticides on the larval stages of trematodes, since they require the aquatic environment to complete their life cycle, meaning greater exposure to contaminants [22,26,34]. The nematode *Caenorhabditis elegans* has emerged as an important model organism in aquatic and soil toxicology research, especially for environmental toxicity assessment of urban areas where water quality is threatened by agricultural activities, sewage and industrial effluents [44]. Moreover, since *C. elegans* is a soil nematode, its use as a model organism can also help elucidate the effects of various pesticides used to control phytonematodes.

An ideal pesticide should have the ability to kill a single target pest without harming non-target organisms, including free-living stages of trematodes. Recently, Monte et al. [22], showed the effect of the commercial formulation of the herbicide glyphosate, Roundup®, on different developmental stages of the trematode *E. paraensei*, both *in vitro* and *in vivo*, using concentrations below that recommended by the manufacturer. In this study, it was possible to observe that all stages (eggs, miracidia, cercariae, newly excysted larvae and adult helminths) presented concentration-dependent mortality when exposed to the Roundup® under experimental conditions, highlighting the possibility of herbicide interference in the transmission dynamics of the parasite.

The miracidial and cercarial stages, which need aquatic environments to reach the intermediate host, showed high mortality when exposed to Roundup® *in vitro*, particularly the miracidial stage. This may be related to the fact that the cercariae are covered by glycocalyx, which coats the tegument and may act as a physical barrier to Roundup® [45], while miracidia have epidermal plates with interepidermal spaces, which can facilitate the herbicide's penetration [46]. It has also been suggested that the herbicide influences the neuromuscular system and energetic metabolism of these larval stages, affecting the success of transmission. Moreover, adult helminths presented a concentration-dependent mortality, which can be related to the possible cell damage caused by the surfactant POEA, which it is believed to be more toxic than the active ingredient [47-50].

The neurodegenerative effects caused by herbicides containing glyphosate and fungicides containing Mn was observed by Negga et al. [51,52], using the nematode *C. elegans* as a model organism to analyze the relationship of pesticide usage and the incidence of Parkinson`s disease. They observed a reduction of neurons due to chronic exposure. McVey et al. [53], also performed a study with *C. elegans* to analyze if unhatched worms exposed to a glyphosate-containing herbicide during the egg stage show abnormal neurodevelopment after hatching. The results indicated statistically significant decrease in neurons and increase in superoxide levels, suggesting that early exposure to the herbicide can impair neuronal development of helminths and that exposure to toxic substances such as pesticides during development may cause individuals to be susceptible to neurodegenerative diseases later in life.

An interesting strategy to assess the real toxicity of active ingredients on helminths would be to conduct *in vitro* tests comparing the effects of its alone and the commercial formulation, in order to analyze the possibility to reduce damage to non-target organisms.

Effects on plant-parasitic nematodes

Plant parasitic nematodes are small, soil-borne pathogens responsible for causing damage in agricultural crops, with estimated losses of US$ 80 billion per year [54]. There are over than 4,100 species of nematodes, displaying a variety of interactions with their hosts. These helminths can be migratory ectoparasites, migratory endoparasites, or semi-endoparasitic nematodes [55]. The most economically important are the root-knot and cyst nematodes, which are biotrophic and equipped with complex feeding structures that are introduced in the roots of their host, allowing them to have a rich and long-lasting food source [56]. Over the years, some chemicals have been employed to control these nematodes, especially fumigant nematicides (methyl bromide), but their uses have been restricted because they can be harmful to the environment and non-target organisms [57,58]. The search for alternative control measures to replace conventional nematicides is a global concern, justifying research of natural substances because of their possible efficiency and lower environmental damage [59-62].

The southern root-knot *Meloidogyne incognita* is the most important plant parasitic nematode species and can attack more than 3,000 agricultural crops, resulting in significant yield losses. Cheng et al. [63], tested the effect of the biological insecticide emamectin benzoate, which is derived from naturally occurring avermectin molecules isolated from the soil bacterium *Streptomyces avermitilis*, on the management of *M. incognita* in laboratory, greenhouse and field experiments. In all trails, emamectin benzoate showed good efficacy against *M. incognita* without damaging the growth of plants. More recently, Martins & Santos [62], analyzed the nematicidal effect of different plant extracts on *M. incognita.* They observed high nematicidal activity with citronella grass and mint extracts (70%) and total mortality with watercress extracts. After exposure, the larvae that remained active were inoculated on tomato seedlings to evaluate their infectivity and the toxic effect of these extracts on the parasitic nematodes was confirmed.

Another alternative to replace synthetic nematicides is the use of plants or their secondary metabolites as sources of nematicidal extracts. The 1,2-dehydropyrrolizidine alkaloids (PAs) are a group of secondary plants metabolites that have the function of protecting plants by repelling vertebrates, insects, snails and even soil-borne nematodes, although some studies have demonstrated that nematodes are not repelled by them but that plants can suppress nematode reproduction [64-74]. Thoden et al. [64], showed the significant reduction of northern root-knot nematode *Meloidogyne hapla* in infested soils through cultivation and incorporation of plants that produce PAs. Additionally, Thoden et al. [65], carried out a study to elucidate the effects of these plant metabolites on the performance of both plant-parasitic and free-living nematodes. The results showed the ovicidal, nematicidal and repellent effects induced by PAs in different nematodes and this toxicity was related to the structural types of PAs. These plant metabolites are considered a promising alternative for nematode management.

DISCUSSION & CONCLUSION

Environmental stresses, such as pollution caused by pesticides, have diverse effects both for humans and the environment. Little research has been done about the effects of these contaminants on helminths. Instead, the focus has mainly been on other organisms considered more exposed to pesticides, such as birds, fish and amphibians [75-80]. The effects of glyphosate-based herbicides on survival, development, sex ratio and growth of wood frogs under laboratory conditions were demonstrated by Navarro-Martín et al. [78], and Lanctôt et al. [79], showing the influence of these chemicals on metamorphosis by altering mRNA gene profiles, although studies in natural systems are needed to corroborate these findings. These results suggest that in addition to host immunity, other biological factors can affect the host-parasite interaction and contribute to amphibian population decline from exposure to pesticides.

The use of helminths under experimental conditions has been useful since it is possible to elucidate physiological, biological and morphological effects caused by pesticides. The most common research topic is the biological effects on the larval stages of trematodes [22,26,34] and phytonematodes [61-63]. In the latter case, studies with these nematodes are used to obtain alternative control/management using PAs, which that are less toxic to the environment than the conventional substances. Repellent effects caused by PAs were observed by Thoden et al. [65], for *Rhabditis* adult's nematodes, but no repellency was observed for *M. incognita* juveniles. In addition, juvenile forms of *M. hapla* were not able to complete their life cycle or their reproduction was reduced when PA-producing plants were infested by this species, impacting host-parasite interaction as well [64]. These findings provide further evidence that differences in the susceptibility are strongly related to different species and different chemical forms of PAs. The adult stages of helminths have great value since they can show the physiological and ultrastructural impacts of pesticides, such as at the nervous and cellular level, which also could contribute to control/management of these parasites by discovering the mode of action of these substances or elucidating the possible interference in the transmission dynamics of helminths.

This mini review has discussed the interface of helminths and pesticides, highlighting how these compounds can affect this biological interaction, particularly parasitic trematodes, soil nematodes and plant-parasitic nematodes. It is important to carry out studies to discover new strategies that minimize toxicity of the compounds currently used, focusing a more specific mechanism of action on the target organisms, and clarify the relevance on the helminths transmission.

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