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REVIEW ARTICLE

A review on the ecotoxicity of macrocyclic lactones and benzimidazoles on aquatic organisms

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Abstract

Despite its wide production and several applications, veterinary antiparasitics from macrocyclic lactones and benzimidazole classes have not received much scientific attention concerning their environmental risks. Thus, we aimed to provide insights into the state of the environmental research on macrocyclic lactone and benzimidazole parasiticides, emphasizing their toxicity to non-target aquatic organisms. We searched for relevant information on these pharmaceutical classes on PubMed and Web of Science. Our search yielded a total of 45 research articles. Most articles corresponded to toxicity testing ($n = 29$), followed by environmental fate ($n = 14$) and other issues ($n = 2$) of selected parasiticides. Macrocyclic lactones were the most studied chemical group (65% of studies). Studies were conducted mainly with invertebrate taxa (70%), with crustaceans being the most predominant group ($n = 27$; 51%). *Daphnia magna* was the most used species ($n = 8$; 15%). Besides, it also proved to be the most sensitive organism, yielding the lowest toxicity measure (EC_{50} 0.25 µg/L for decreased mobility after 48 h-abamectin exposure) reported. Moreover, most studies were performed in laboratory settings, tracking a limited number of endpoints (acute mortality, immobility, and community disturbance). We posit that macrocyclic lactones and benzimidazoles warrant coordinated action to understand their environmental risks.

Keywords Agriculture · Aquatic toxicity · *Daphnia magna* · Emerging contaminants · Environmental risk assessment · Veterinary antiparasitics

Introduction

As concerns over medicines in the environment grew, Boxall et al. (2003) discussed the role of veterinary pharmaceuticals, their potentially novel routes of contamination, and the significant gaps to be filled to identify and address their environmental risks. Veterinary pharmaceuticals reach aquatic environments through routes that depend on the production system in which they are used, as well as the host being treated and the route of administration. Examples of higher-risk activities are net pan enclosures at fish farming facilities and treatment of grass-fed cattle near water bodies, which are made greater when applied to large-scale herds (Kim et al. 2008a, b; Di Nica et al. 2015).

Within the broader category of veterinary pharmaceuticals, antiparasitics (also referred to as parasiticides) are drugs used to control parasites such as helminths and ticks. They present features that may characterize their environmental relevance. These chemicals reach the environment through novel routes described for veterinary

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Highlights
- Most articles corresponded to toxicity testing.
- The macrocyclic lactone emamectin was the most studied parasiticide.
- Invertebrates were the most used group of organisms.
- *Daphnia magna* was the most used organism, in addition to being considered the most sensitive.

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pharmaceuticals at large, but in large volumes and causing detrimental effects comparable to antibiotics (Kools et al. 2008; Di Nica et al. 2015). The agricultural landscape is particularly important for the environmental risks posed by the large-scale use of veterinary antiparasitics (Kools et al. 2008; Di Nica et al. 2015). Plagues such as ticks, fleas, flies, and helminths are a continuous threat of financial loss in livestock production systems, so they must be closely controlled, leading to prophylactic and constant use of parasiticides (Kornele et al. 2014; French 2018). In the absence of specific limiting regulations, these drugs may be extensively and indiscriminately used, exerting high levels of xenobiotic-related stress on aquatic organisms in nearby ecosystems (Vieira et al. 2019).

Among the most relevant antiparasitic agents in agriculture, the classes of macrocyclic lactones (MLs) and benzimidazoles (BZs) stand out. MLs, including milbemycins and avermectins, are parasiticides and insecticides that are produced through fermentation by soil-dwelling microorganisms and have been used as insecticides and acaricides for crop protection or parasiticides for animal health. Ivermectin is the first ML that was released for use in both humans and animals and has shown both excellent efficacy and high tolerability in the treatment of parasite infestations. Other MLs, such as abamectin, emamectin, and moxidectin, were subsequently commercialized (Yang 2012). In turn, BZs are broad-spectrum nematocides, with some drugs also having activity against flukes and tapeworms. Fenbendazole is a well-known BZ that is effective against the protozoan parasite Giardia. Many BZs kill larval stages of nematodes as well as adults, but usually, larval efficacy is lower than for adults (Kaplan 2009).

Considering the large number of animals used in major cattle-producing countries, veterinary antiparasitics warrant attention. In 2018, flea and tick medications accounted for 29.4% of the US animal health market (Pham and Donovan 2018), while antiparasitics have been the most important therapeutic class in the Brazilian animal health market since 2015, having surpassed antibiotics in 2014 (SINDAN 2019). This is in line with the arguments used by Wardhaugh (2005) to draw attention to parasiticides used in livestock production, warning of the need for usage information and the potential risks to non-target organisms in dung and pasture. Since then, other such calls for research on the matter have appeared in the literature (Loeb 2018; Powell et al. 2018).

Parasiticides are often not fully metabolized and are excreted via urine and feces by treated animals. For example, ivermectin is only partially metabolized by the liver and then excreted mostly through the feces between 40 and nearly 80% (Halley et al. 1989; Chiu et al. 1990; Lifschitz et al. 2000). Many antiparasitics are also available in formulations for external use (*e.g.*, pastes, sprays, aspersion, and baths) to treat ectoparasites such as fleas, ticks, and flies. In these cases, metabolization is irrelevant, as the compounds may reach nearby ecosystems via wash-off. For aquatic environments, common pollution routes include direct deposition by animals reared in the pasture (Boxall et al. 2003), lixiviation to nearby bodies of water, and incorrect waste disposal (Kim et al. 2008a, b). Drugs used in aquacultures such as emamectin benzoate and teflubenzuron are particularly concerning in the area around facilities, possibly reaching (Bloodworth et al. 2019).

Once they reach aquatic ecosystems through such routes, these drugs exert a several ecotoxicological effects. In an extensive review that aimed to assess the non-target effects of MLs in aquatic and terrestrial environments, Lumaret et al. (2012) discussed a tendency for these compounds to be more toxic to aquatic invertebrates, especially during early life stages. In addition, Carlsson et al. (2013) sought to assess the adverse effects of 15 veterinary pharmacists (10 antiparasitic and 5 antibiotics) on zebrafish embryos and observed several endpoints such as mortality, malformations, and other sublethal responses, suggesting that this high toxicity may extend to early developmental stages of fish. This may be a product of the evolutionary relationships bootstrapping the parasite, the host, and the non-target species (Brady et al. 2017), as many of these chemicals disrupt conserved structures present in target parasites (mainly arthropods and helminths), as well as in non-target organisms (Anadón et al. 2009; Akre 2016; Zhang et al. 2020).

Historically, greater attention has been paid to the ecotoxicological risk of antibiotics (*i.e.*, chemicals active against bacteria) rather than antiparasitic agents. Both have similarities in terms of mechanisms of combating target organisms, such as how they can affect cell integrity. However, antibiotics and antiparasitics differ with regard to the mechanisms of action. For antibiotics, the mechanisms can be classified according to the target site and the structural alterations promoted (Lorian 1999). Among the main ones are: inhibition of cell wall synthesis or nucleic acid synthesis, inhibition of ribosomal or cell membrane function, and inhibition of folate metabolism (Dowling et al. 2017). Antiparasitics such as the BZ class act by preventing the dimerization of α-tubulin, consequently preventing the polymerization of microtubules, which generates loss of function in various parts of the cell (Alves and Barbosa 2018). In turn, MLs act on the central nervous system, causing hyperpolarization of neurons and inhibition of the passage of nervous stimuli, resulting in flaccid paralysis (Spinosa et al. 2008; Rosa et al. 2016).

Despite the large volume of use of MLs and BZs and their potential ecotoxicological risks, studies on these antiparasitic drugs are still scarce, especially those considering their effects on aquatic organisms. Accordingly, the current study aimed to provide a preliminary picture of the role of MLs and BZs as environmental toxicants in aquatic environments.

We use a systematic review as a stepping stone to examine these chemical groups as separate chemical entities regarding their risks to aquatic wildlife. Data concerning the bibliometric parameters (*i.e.*, number of articles, geographical distribution, number of citations, and impact factor), exposure conditions, species, effects on non-target organisms, toxicity parameters, type of samples taken in environmental fate studies, and detection methods were summarized and discussed. Also, articles were arranged into three categories according to their objectives and information provided, namely: (i) toxicity testing, (ii) environmental fate, and (iii) others. Furthermore, several research gaps and recommendations for future research are also presented.

Materials and methods

Using PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com), we gathered the scientific articles retrieved between August 2021 and November 2022 by the following 24 keyword combinations (see Table S1). The combinations were as follows: (i) "veterinary antiparasitic" and "aquatic environment"; (ii) "veterinary parasiticide" and "aquatic environment"; (iii) "veterinary antiparasitic," "aquatic," and "non-target"; (iv) the name of each antiparasitic of the classes under study with "aquatic," "non-target," and/or "aquatic environment." The articles retrieved were curated by the following inclusion and exclusion criteria:

i) Inclusion criteria: studies on compounds used to treat parasites in animals, toxicity to aquatic organisms, risk assessment contributions, studies on environmental samples (*e.g.*, biological tissue, sediment, and water), and peer-reviewed literature.
ii) Exclusion criteria: studies on other classes of antiparasitics (*e.g.*, organophosphates), studies on other pharmaceutical groups (*e.g.*, antibiotics), efficacy studies, clinical cases, analysis of products for human consumption, review papers, technical reports, protocols, studies in languages other than English, and non aquatic organisms.

The included papers were then scanned for relevant information, which included their objective, chemicals and organisms studied, exposure conditions, effects observed, toxicity metrics (LC_{50}, EC_{50}, and NOEC), type of samples taken in environmental fate studies, and detection method. The geographical location of study was identified from the mailing address of the corresponding author. To quantitatively record the data retrieved from toxicity studies, we used an entry system in which one entry equals the study of one chemical in a single organism. In this manner, one paper may correspond to one or more entries, depending on how many chemicals and how many organisms it investigated.

Results and discussion

Overview

The combinations of keywords in Pubmed yielded a total of 150 unique results, of which only 40 were left once the inclusion/exclusion criteria were applied. While on the Web of Science, 26 articles were found with the combinations, leaving only 9 after the inclusion/exclusion criteria. After that, it was possible to observe 4 articles that were in the two databases, with 45 articles remaining in total. These articles were arranged into three categories according to their objectives and information provided, namely: toxicity testing (Table 1), environmental fate (Table 2), and others (Table 3). This third category was necessary to accommodate relevant information that did not fit into toxicity or environmental fate studies. It comprised one paper about the uptake and depuration kinetics of selected veterinary pharmaceuticals in blue mussels (Brooks et al. 2019) and one related to environmental risk assessment (Liebig et al. 2010).

These results provide a robust framework for discussion since they encompass a highly diverse set of methods, test organisms, and chemical compounds. Prominently, the high number of test organisms (representing a few major biological groups) and the diversity of chemical classes allowed for discussions of taxa-specific toxicity.

Bibliometrics

The first study involving at least one of the classes of parasiticides targeted by this review was published in 2005 by Löffler and collaborators, covering the environmental fate of several pharmaceuticals, including ivermectin. Since then, few works were published in the following years until 2010 (Fig. 1A). From this year onwards, there has been an increase in the number of published works. The beginning of studies with antiparasitics coincides with the increasingly constant reports on the presence of emerging contaminants in water reservoirs in the USA (Halden 2010). This provided a strong stimulus for research on the effects of pesticides, pharmaceuticals, and other micropollutants on aquatic organisms.

Studies were carried out by research groups from 19 countries, mainly by Germany ($n=7$; 16%) and China ($n=6$; 13%), followed by Brazil, Poland, and Belgium ($n=4$; 9% each) (Fig. 1B). Similarly, Saiki et al. (2021) showed that Germany stands out in studies concerning the sediment toxicity assessment using zebrafish (*Danio rerio*). Besides, it is

Table 1 Studies of the toxicity of lactone macrocyclic and benzimidazol drugs to non-target organisms

Reference	Compound	Organism	Exposure conditions	Exposure period	Effect studied	Observed effect (EC_{50}/LC_{50}/NOEC)
Tisler and Kozuh Erzen 2006	Abamectin	*Scenedesmus subspicatus*	Laboratory settings (ISO 8692, 1989)	72 h	Growth	EC_{50} (72 h) = 44 µg/L
Tisler and Kozuh Erzen 2006	Abamectin	*Daphnia magna*	Laboratory settings (OECD 211, 1998)	Acute: 48 h Chronic: 21 days	Immobility, mortality, and reproduction	EC_{50} (48 h, decreased of mobility) = 0.25 µg/L (21 days NOEC) = 0.0047 µg/L
Tisler and Kozuh Erzen 2006	Abamectin	*Danio rerio*	Laboratory settings (ISSO 7346–1/ ISSO 7346-2, 1996)	96 h	Mortality and swimming activity	EC_{50} (24 h, decreased swimming) = 50.4 µg/L
Santos et al. 2023	Abamectin	*Danio rerio* (adult)	Laboratory settings: acute toxicity test (FET) (OECD 236)	Acute: 96 h Chronic: 15 days	Toxicity	LC_{50} = 105.68 µg/L
Falkenberg et al. 2017	Abamectin	*Crassostrea gigas*	Laboratory settings: exposure occurred at 5 different concentrations to assess sperm motility, fertilization success, and larval development	24 h	Toxicity and reproduction	LOEC (reproductive toxicity parameters) = 1000 µg/L, 500 µg/L, and 100 µg/L; CE_{50} (reproductive toxicity parameters) = 934 µg/L, 1076.26 µg/L, and 140 µg/L
Huang et al. 2020	Abamectin	*Eriocheir sinensis* (hemocytes)	Laboratory settings: hemocytes were exposed to three concentrations (2 µM, 5 µM, and 10 µM). Cell viability was determined by the CCK-8 method	6 h, 12 h, and 24 h intervals	Cell viability, phagocytic activity, immune enzyme activities, and ROS generation	n.d
Reinwald et al. 2022	Abamectin	*Danio rerio*	Laboratory settings: zebrafish embryos were exposed to three sublethal concentrations according to the acute toxicity test (FET) (OECD 236), with modifications	96 h	Transcriptional analysis	n.d
Weichert et al. 2017	Abamectin	*Danio rerio*	Laboratory settings: acute toxicity test (FET) (OECD 236) was performed using 10 different concentrations	96 h	Toxicity	LOEC for hyperactivity = 0.22 mg/L; LOEC for hypoactivity: 0.63 mg/L; NOEC: 0.10 mg/L

Table 1 (continued)

Reference	Compound	Organism	Exposure conditions	Exposure period	Effect studied	Observed effect (EC_{50}/LC_{50}/NOEC)
Santos et al. 2023	Abamectin	*Danio rerio*	Laboratory settings: acute toxicity test (FET) (OECD 236)	Acute exposure: 96 h Chronic exposure: 15 days	Toxicity	LC_{50} = 105.68 µg/L
Kołodziejska et al. 2013	Doramectin	*Vibrio fischeri*	Laboratory settings (DIN 38412-L34, 1991)	30 min	Luminescence inhibition	EC_{50} = not reached
Kołodziejska et al. 2013	Doramectin	*Scenedesmus vacuolatus*	Laboratory settings (ISO 8692, 1989)	24 h	Inhibition of algal reproduction	EC_{50} = not reached
Kołodziejska et al. 2013	Doramectin	*Lemna minor*	Laboratory settings: measurement of growth rate inhibition determined by leaf area, which was calculated for treated plants versus untreated controls	3 days	Growth inhibition	EC_{50} = not reached
Carlsson et al. 2018	Doramectin	*Danio rerio*	Laboratory settings: exposure occurred using three concentrations with 24 embryos each. Larval swimming activity was recorded using the Zebrabox	6 days	Swimming activity	n.d
Alak et al. 2017	Eprinomectin	*Rainbow trout*	Laboratory settings: methods such as Elisa and techniques based on photocolorimetry	96 h	Tanscriptional changes and activity of antioxidant enzymes	Decreased SOD, CAT, 8-OhdG, and GPx activities in the liver
Puckowski et al. 2017	Fenbendazole	*Daphnia magna*	Laboratory settings: the immobilization test has been evaluated using DAPHTOXKIT. Tests were carried out with isolated and mixed substances	48 h	Immobility and toxicity	EC_{50} Fen = 0.0193; EC_{50} mixture A (5:5) 0.0278 mg/L; EC_{50} mixture B (7:3) 0.0304 mg/L; EC_{50} mixture C (3:7) 0.0212 mg/L
Carlsson et al. 2018	Fenbendazole	*Danio rerio*	Laboratory settings: exposure occurred using three concentrations with 24 embryos each. Larval swimming activity was recorded using the Zebrabox	6 days	Swimming activity	n.d
Bundschuh et al. 2016	Fenbendazole	*Dugesia gonocephala*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 44.2 µg/L

Table 1 (continued)

Reference	Compound	Organism	Exposure conditions	Exposure period	Effect studied	Observed effect (EC_{50}/LC_{50}/NOEC)
Bundschuh et al. 2016	Fenbendazole	*Caenorhabditis elegans*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (24 h) ≥ 1000 µg/L
Bundschuh et al. 2016	Fenbendazole	*Brachionus calyciflorus*	Laboratory settings: (ASTM E1440, 1998)	Between 24 and 96 h	Immobility and toxicity	EC_{50} (24 h) ≥ 8000 µg/L
Bundschuh et al. 2016	Fenbendazole	*Tubifex tubifex*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 32.0 µg/L
Bundschuh et al. 2016	Fenbendazole	*Radix ovata*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 1000 µg/L
Bundschuh et al. 2016	Fenbendazole	*Daphnia magna*	Laboratory settings: (OECD 202, 2004)	Between 24 and 96 h	Immobility and toxicity	EC_{50} (48 h, most sensitive organism) = 16.7 µg/L
Bundschuh et al. 2016	Fenbendazole	*Gammarus pulex*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 146.4 µg/L
Bundschuh et al. 2016	Fenbendazole	*Asellus aquaticus*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = > 1000 µg/L
Bundschuh et al. 2016	Fenbendazole	*Radix ovata*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 1000 µg/L
Wagil et al. 2015a, b	Fenbendazole	*Vibrio fischeri*	Laboratory settings: (DIN 38412-L34, 1991)	30 min	Luminescence inhibition	EC_{50} (48 h, no effect on luminescence) = 300 µg/L
Wagil et al. 2015a, b	Fenbendazole	*Lemna minor*	Laboratory settings: measurement of growth rate inhibition determined by leaf area	3 days	Growth inhibition	EC_{50} (48 h, no effect on growth) = > 1000 µg/L
Wagil et al. 2015a, b	Fenbendazole	*Daphnia magna*	Laboratory settings: (OECD 202, 2004)	48 h	Immobilization	EC_{50} (48 h, most sensitive organism) = 19 µg/L
Wagil et al. 2015a, b	Fenbendazole	*Scenedesms vacuolatus*	Laboratory settings: (ISO 8692, 1989)	96 h	Gene expression and biomarker activity	LC_{50} = 93.5 µg/L
Park et al. 2009	Fenbendazole	*Chironomus riparius larvae*	Laboratory settings: using RT-PCR for gene expression. Spectrophotometry for enzymes	96 h	Gene expression and biomarker activity	LC_{50} = 93.5 µg/L
Bundschuh et al. 2016	Flubendazole	*Dugesia gonocephala*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h, immobility) = 21.9 µg/L (most sensitive)
Bundschuh et al. 2016	Flubendazole	*Caenorhabdis elegans*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (24 h, immobility) = > 1000 µg/L
Bundschuh et al. 2016	Flubendazole	*Brachionus calyciflorus*	Laboratory settings: (ASTM E1440)	Between 24 and 96 h	Immobility and toxicity	EC_{50} (24 h, immobility) = > 8000 µg/L
Bundschuh et al. 2016	Flubendazole	*Tubifex tubifex*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h, immobility) = 22.1 µg/L

Table 1 (continued)

Reference	Compound	Organism	Exposure conditions	Exposure period	Effect studied	Observed effect (EC_{50}/LC_{50}/NOEC)
Bundschuh et al. 2016	Flubendazole	*Radix ovata*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h, immobiliy) = 1000 µg/L
Bundschuh et al. 2016	Flubendazole	*Daphnia magna*	Laboratory settings: (OECD 202, 2004)	Between 24 and 96 h	Immobility and toxicity	EC_{50} (48 h) = 70.1 µg/L
Bundschuh et al. 2016	Flubendazole	*Gammarus pulex*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 105.4 µg/L
Bundschuh et al. 2016	Flubendazole	*Asellus aquaticus*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = > 1000 µg/L
Wagil et al. 2015a, b	Flubendazole	*Vibrio fischeri*	Laboratory settings: (DIN 38412-L34, 1991)	30 min	Luminescence inhibition	EC_{50} (48 h, luminescence) = 300 µg/L
Wagil et al. 2015a, b	Flubendazole	*Scenedesmus vacuolatus*	Laboratory settings: (ISO 8692, 1989)	24 h	Inhibition of algal reproduction	EC_{50} (48 h, growth) = > 1000 µg/L
Wagil et al. 2015a, b	Flubendazole	*Lemna minor*	Laboratory settings: measurement of growth rate inhibition determined by leaf area, which was calculated for treated plants versus untreated controls	3 days	Growth inhibition	EC_{50} (48 h, no effect on growth) = > 1000 µg/L
Puckowski et al. 2017	Flubendazole	*Daphnia magna*	Laboratory settings: the immobilization test has been evaluated using DAPHTOXKIT. Tests were carried out with isolated and mixed substances	48 h	Immobility and toxicity	EC_{50} flu = 0.0448 mg/L; EC_{50} mixture A (5:5) 0.0278 mg/L; EC_{50} mixture B (7:3) 0.0304 mg/L; EC_{50} mixture C (3:7) 0.0212 mg/L
Babić et al. 2018	Febantel	Vibrio *fischeri*	Laboratory settings: the toxicity was evaluated using the standard bioluminescent method ISO 11348–2:2007 of short duration	30 min	Luminescence inhibition	n.d
Bundschuh et al. 2016	Ivermectin	*Dugesia gonocephala*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 675.2 µg/L
Bundschuh et al. 2016	Ivermectin	*Caenorhabditis elegans*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (24 h) = 17.5 µg/L
Bundschuh et al. 2016	Ivermectin	*Brachionus calyciflorus*	Laboratory settings: (ASTM E1440, 1998)	Between 24 and 96 h	Immobility and toxicity	EC_{50} (24 h) = 1961 µg/L
Bundschuh et al. 2016	Ivermectin	*Tubifex tubifex*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 1866 µg/L

Table 1 (continued)

Reference	Compound	Organism	Exposure conditions	Exposure period	Effect studied	Observed effect (EC_{50}/LC_{50}/NOEC)
Bundschuh et al. 2016	Ivermectin	*Radix ovata*	Laboratory setting: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 17 µg/L
Bundschuh et al. 2016	Ivermectin	*Daphnia magna*	Laboratory settings: (OECD 202, 2004)	Between 24 and 96 h	Immobility and toxicity	EC_{50} (48 h, highly toxic) = 0.59 µg/L
Bundschuh et al. 2016	Ivermectin	*Gammarus pulex*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h, highly toxic) = 1.4 µg/L
Bundschuh et al. 2016	Ivermectin	*Asellus aquaticus*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 390.3 µg/L
Bundschuh et al. 2016	Ivermectin	*Amphinemura sulcicollis*	Laboratory settings: static acute exposure	Between 24 and 96 h	Immobility and toxicity	EC_{50} (96 h) = 14.3 µg/L
Boonstra et al. 2011	Ivermectin	*Ceriodaphnia* sp.	Microcosm	42 days	Community abundance and acute toxicity	NOEC (6 days, most sensitive) = 0.03 µg/L
Boonstra et al. 2011	Ivermectin	*Chydorus sphaericus*	Microcosm	42 days	Community abundance and acute toxicity	NOEC (significant reductions) = 0.1 µg/L
Boonstra et al. 2011	Ivermectin	*Daphnia longispina*	Microcosm	42 days	Community/abundance and acute toxicity	NOEC (significant reductions) = 0.3 µg/L
Boonstra et al. 2011	Ivermectin	*Cyclopoida* nauplii	Microcosm	42 days	Community abundance and acute toxicity	NOEC (6–13 days, significant reductions) = 1 µg/L
Boonstra et al. 2011	Ivermectin	*Cephalodella* sp.	Microcosm	42 days	Community abundance and acute toxicity	NOEC (no effects) = 1 µg/L
Boonstra et al. 2011	Ivermectin	*Lecane* group *lunaris*	Microcosm	42 days	Community abundance and acute toxicity	NOEC = 3 µg/L
Boonstra et al. 2011	Ivermectin	*Polyarthra remata*	Microcosm	42 days	Community abundance and acute toxicity	NOEC = 3 µg/L
Boonstra et al. 2011	Ivermectin	*Lecane* group *luna*	Microcosm	42 days	Community abundance and acute toxicity	NOEC = 3 µg/L
Boonstra et al. 2011	Ivermectin	*Brachionus quadridentatus*	Microcosm	42 day	Community abundance and acute toxicity	NOEC = 3 µg/L
Boonstra et al. 2011	Ivermectin	*Trichocerca* group *porcellus*	Microcosm	42 days	Community abundance and acute toxicity	NOEC = 3 µg/L
Boonstra et al. 2011	Ivermectin	*Keratella quadrat*	Microcosm	42 days	Community abundance and acute toxicity	NOEC = 3 µg/L
Boonstra et al. 2011	Ivermectin	*Synchaeta* sp.	Microcosm	42 days	Community abundance and acute toxicity	NOEC = 3 µg/L
Brinke et al. 2010	Ivermectin	Ostracoda	Indoor microcosm	224 days	Abundance in meiobenthic community	n.d
Brinke et al. 2010	Ivermectin	Cladocera	Indoor microcosm	224 days	Abundance in meiobenthic community	NOEC (meiofauna, 26 and 56 days) = 6.2 µg/L

Table 1 (continued)

Reference	Compound	Organism	Exposure conditions	Exposure period	Effect studied	Observed effect (EC_{50}/LC_{50}/NOEC)
Brinke et al. 2010	Ivermectin	Nematoda	Indoor microcosm	224 days	Abundance in meiobenthic community	NOEC (community, 7–28 days) = 0.6 µg/L
Brinke et al. 2010	Ivermectin	Tardigrada	Indoor microcosm	224 days	Abundance in meiobenthic community	n.d
Garric et al. 2007	Ivermectin	*Daphnia magna*	Laboratory settings: (OECD 202, 2004)/ (OECD 211, 1998)	48 h	Toxicity, immobility, and reproduction	LC_{50} = 5.7 ng/L; LOEC = 0.001 ng/L; NOEC = 0.0003 ng/L
Garric et al. 2007	Ivermectin	*Pseudokirchneriella subcapitata*	Laboratory settings: (OECD 201, 2002)	72 h	Growth	LOEC = 1250 ng/L; NOEC = 391 ng/L
Udebuani et al. 2021	Pharmaceutical cocktail with ivermetcin	*Pseudokirchneriella subcapitata*	Laboratory settings: (ISO, 8692)	72 h	Growth rate inhibition	n.d
Udebuani et al. 2021	Pharmaceutical cocktail with ivermetcin	*Daphnia magna*	Laboratory settings: (OECD 202, 2004)	48 h	Mortality/immobilization effect	CL_{50} = 79.8 µg/L
Udebuani et al. 2021	Pharmaceutical cocktail with ivermetcin	*Tetrahymena thermophila*	Laboratory settings: (OECD 202, 2004)	24 h	Growth inhibition	EC_{50} = 0.14 µg/L
Lozano et al. 2021	Ivermectin	*Prochilodus lineatus*	Laboratory setting: swimming was analyzed by video recording in each aquarium over 10 min, and spectrophotometry for enzymes	15 days	Biomarkers and swimming	n.d
Nunes et al. 2021	Ivermectin	*Hediste diversicolor*	Laboratory settings: an acute exposure and a chronic exposure were performed using five different concentrations with 1 animal being exposed individually	Acute exposure: 96 h Chronic exposure: 28 days	Behavioral and analysis of biomarkers	n.d
Zhang et al. 2022a, b	Avermectin	*Cyprinus carpio*	Laboratory settings: (OECD 2013)	96 h	Toxicity	LC_{50} = 24.04 µg/L
Zhang et al. 2022a, b	Avermectin	Carp	Laboratory settings: animals were exposed to two concentrations (3.005 µg/L and 12.02 µg/L). Fish spleens were obtained for histopathology analysis and assess biochemical and genetic markers (RT-PCR)	Acute exposition 96 h	Spleen histopathology, analysis of oxidative stress biochemical markers, and transcriptional changes related to inflammation	n.d

Table 1 (continued)

Reference	Compound	Organism	Exposure conditions	Exposure period	Effect studied	Observed effect (EC_{50}/LC_{50}/NOEC)
Song et al. 2016	Emamectin	*Daphnia magna*	Laboratory settings (OECD 202, 2004)	48 h	Mortality and transcriptional changes	NOEC = 7.8 pM; EC_{50} = 143.3 pM
Cheng et al. 2020	Emamectin benzoato	*A. marina*	Microcosm: using tests according to OECD (2004), US-EPA (1994), and OECD (2001)	5 days	Growth and mortality	LC_{50} > 1000 µg/kg; NOEC = ≥ 1000 µg/kg
Cheng et al. 2020	Emamectin benzoato	*C. volutator*	Microcosm: using tests according to OECD (2004), US-EPA (1994), and OECD (2001)	5 days	Growth and mortality	LC_{50} = 316 µg/kg; NOEC = ≥ 1000 µg/kg
Cheng et al. 2020	Emamectin benzoato	*C. edule*	Microcosm: using tests according to OECD (2004), US-EPA (1994), and OECD (2001)	5 days	Growth and mortality	Lc_{50} = > 1000 µg/kg; NOEC = ≥ 1000 µg/kg
Weichert et al. 2017	Emamectin benzoato	*Danio rerio*	Laboratory settings: (OECD 236)	96 h	Toxicity	EC_{50} = 1.19 mg/L; LC_{50} of 25.33 mg/L
Veldhoen et al. 2012	Emamectin benzoate (EB)	*Pandalus platyceros*	Laboratory settings: exposed occurred using different concentrations of EB (0.1–4.8 mg/kg sediment)	8 days	Transcriptional analysis	n.d
Rain-Franco et al. 2018	Emamectin benzoate	*Microbial communities*	Microcosm	6 h incubation	Photoautotrophic and chemoautotrophic carbon fixation	n.d
Mayor et al. 2008	Emamectin benzoate	*Corophium volutator*	Mesocosm using tests according to US EPA (1994), Bat and Raffaelli (1998), and RIKZ (1999)	10 days	Mortality	LC_{50} = 153 µg/kg wet sediment
Mayor et al. 2008	Emamectin benzoate	*Hediste diversicolor*	Mesocosm using tests according to US EPA (1994), Bat and Raffaelli (1998), and RIKZ (1999)	10 days	Mortality	LC_{50} = 1368 µg/kg wet sediment
Mesa et al. 2018	Moxidectin	*Pomacea canaliculata*	Microcosm: the artificial sediment based on OECD 218 (2004)	17 days	Survival and growth	Reduced survival from 250 µg/kg (17 days)

Table 1 (continued)

Reference	Compound	Organism	Exposure conditions	Exposure period	Effect studied	Observed effect (EC_{50}/LC_{50}/NOEC)
Mesa et al. 2018	Moxidectin	*Hyalella curvispina*	Microcosm: the artificial sediment based on OECD 218 (2004)	17 days	Survival and growth	Mortality from 250 µg/kg (7 days)
Mesa et al. 2018	Moxidectin	*Ceriodaphnia dubia*	Microcosm: the artificial sediment based on OECD 218 (2004)	17 days	Survival and growth	No statistically significant effects
Muniz et al. 2021	Moxidectin	*Danio rerio*	Laboratory settings: (OECD 236)	96 h	Toxicity	EC_{50} = 20.75 µg/L

to be expected that in countries like Brazil, where agriculture is a relevant economic activity, there is a greater number of research groups interested in investigating the impacts of products derived from these activities on the environment.

Articles in this area have received great attention. This is revealed in a large number of citations (1.082), highlighting the period between 2008 and 2017 (770) (Fig. 1C). In addition, these works have gained space in the most prestigious journals in Environmental Chemistry, Toxicology and Risk Assessment, with most works ($n = 34$; 76%) having been published in vehicles with an impact factor ≥ 5.0 (Fig. 1D and E).

Macrocyclic lactones and benzimidazoles in numbers

A total of 29 articles on toxicity to non-target organisms were included in this study (Table 1). To provide a more concise analysis, we registered one entry per compound studied in each paper, then we categorized them by chemical group (Figs. 2A and 3). MLs accounted for 68% (61 entries) of the individual entries in toxicity papers, while for BZs were 32% (28 entries) (Fig. 2A and Table 1). As for specific compounds, the most investigated of the MLs was emamectin (15% of entries), while fenbendazole (57% of entries) was the most studied BZ (Table 1).

In the category of environmental fate studies, we had a total count of 14 articles and 35 entries, with MLs appearing in 60% of entries and BZs in 40% (Table 2). Some studies investigated more than one compound: one with fenbendazole and flubendazole (BZs), one with emamectin benzoate (ML), one using three MLs, and another using eight BZs. The studies used a range of analytical chemistry methods to study the properties or presence of the compounds in fish, soil, sediment, water, and/or muscle. The samples were obtained in their respective countries, namely: Argentina, Belgium, Brazil, China, France, Germany, Greece, Morocco, Norway, Poland, and Scotland.

The interest of researchers in the study of MLs and BZs falls in line with the wide use of these major classes of pharmaceuticals. The ML ivermectin is a major parasiticide worldwide, used to treat various diseases such as worm infections in animals and river blindness in humans (Molento 2020). The BZs are also prominent drugs used worldwide to treat parasitic and fungi-related illnesses in humans and animals (Brauer et al. 2019; Porto et al. 2020).

Effects on non-target organisms

While the number of individual studies on toxicity to non-target organisms was limited (29 papers), only 12 of them were single-species investigations. In addition, 2 articles included toxicity data on 9 organisms or more, which

Table 2 Studies on the environment fate of veterinary antiparasitics

Reference	Compound	Sample settings	Quant. method	Key observations
Dionisio and Rath 2016 1	Abamectin	Soil: studies were conducted on sandy, sandy–clay and clay soils from São Paulo, Brazil	HPLC-FLD	High sorption capacity, limited mobility; dissipation mainly by microbial degradation (up to 4 days)
Heinrich et al. 2021 2	Abamectin	Sediment and soil: from a pool of samples, 17 were selected for studies based on the OECD	HPLC-fluorescence	Distribution coefficients in sediment (KD); 38–642 mL/g; (KD) in soil: 38 a 211 mL/g
Heinrich et al. 2021	Doramectin	Sediment and soil: from a pool of samples, 17 were selected for studies based on the OECD	HPLC-fluorescence	Distribution coefficients (KD) in sediment: 38–642 mL/g; (KD) in soil: 63 a 428 mL/g
Bloodworth et al. 2019	Emamectin benzoate	Sediment near fish farms (field study): sediment samples were collected from the Scottish seabed for chemical and ecological analysis	LC–MS/MS	Found in 97% of samples; above 0.763 µg/kg* in 7% of samples taken > 100 m from the cages
Litskas et al. 2013	Eprinomectin	Soil (laboratory settings): mixed soil samples were collected, air-dried, and further studied using the OECD (2002) 307 protocol	HPLC-FLD	Eprinomectin is resistant to dissipation in the soils tested and in cattle manure
Charuaud et al. 2019	Eprinomectin	Water: water resource samples were collected from 25 sites (23 surface waters and two groundwaters) used for tap water production and located in watersheds	(RRLC-MS/MS)	Concentrations from 7 up to 45 ng/L)
Wagil et al. 2015a, b	Fenbendazole	Water, sediment, and fish tissues (field study)	(RRLC-MS/MS)	Water: up to 39.2 ng/L (autumn); sediment: up to 4.4 ng/g (autumn)
Wagil et al. 2015a, b	Flubendazole	Water, sediment, and fish tissues (field study)	LC–MS/MS	Flubendazole is resistant to dissipation in the soils tested and in cattle manure
Rath et al. 2016	Ivermectin	Soil: two soil samples were collected in two brazilian cities (laboratory settings)	HPLC–DAD, HPLC-FLD	High sorption capacity to soils tested; difficult to desorb; quickly degraded in both sandy and clay soil
Mesa et al. 2020	Ivermectin	Sediment and water: surface water and sediment samples were collected in triplicate	HPLC	Total concentration of IVM in the wetlands, and concentration in cattle manure, sediment, and water increased with the number of treated cattle and frequency of IVM injections
Heinrich et al. 2021	Ivermectin	Sediment and soils: were examined 20 soil samples and six sediments	HPLC-fluorescence	Distribution coefficients (KD) in sediment: 38–642 mL/g; (KD) in soil: 76 a 642 ml/g
Charuaud et al. 2019	Ivermectin	Water: water resources samples were collected from 25 sites	(RRLC-MS/MS)	Similar concentrations with other studies
Charuaud et al. 2019	Tricabendazole	Water: water resources samples were collected from 25 sites	RRLC-MS/MS	Concentrations of its metabolites were observed
Chen et al. 2021	Albendazole	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	The detection rate were the highest (100%), with concentrations ranging from 0.40 to 10.92 ng/L (mean 1.59 ng/L), respectively

Table 2 (continued)

Reference	Compound	Sample settings	Quant. method	Key observations
Chen et al. 2021	Ricobendazole	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	The detection rate also were the highest (100%), with concentrations ranging from 3.22 to 61.12 ng/L (mean 9.44 ng/L)
Chen et al. 2021	Fenbendazole	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	1.04 ng/L were detected in the river
Chen et al. 2021	Flubendazole	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	1.09 ng/L were detected in the river
Chen et al. 2021	Mebendazole	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	2.81 ng/L were detected in the river
Chen et al. 2021	Oxfendazole	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	0.71 ng/L were detected in the river
Chen et al. 2021	Thiabendazole	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	0.54 ng/L were detected in the river
Chen et al. 2021	Abamectin	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	Macrocyclic lactones were low in the water. The results might be mainly explained by their relatively high Pseudo-partitioning coefficient
Chen et al. 2021	Thiabendazole	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	0.54 ng/L were detected in the river
Chen et al. 2021	Doramectin	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	Macrocyclic lactones were low in the water. The results might be mainly explained by their relatively high pseudo-partitioning coefficient
Chen et al. 2021	Eprinomectin	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	Macrocyclic lactones were low in the water. The results might be mainly explained by their relatively high pseudo-partitioning coefficient
Chen et al. 2021	Ivermectin	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	Macrocyclic lactones were low in the water. The results might be mainly explained by their relatively high pseudo-partitioning coefficient
Chen et al. 2021	Moxidectin	Water and sediment: samples were detected in triplicate	UHLPC-MS/MS	Macrocyclic lactones were low in the water. The results might be mainly explained by their relatively high Pseudo-partitioning coefficient
Wang et al. 2019	Ivermectin	Water, sediment, and aquatic organisms (invertebrates, aquatic plants, and fish)	Elisa KIT	The concentration of IVM in the water after the addition was 0.092 ng/mL, reaching 0.076 ng/mL in 70 days The concentration of IVM in the sediment reached 3.141 ng/g at 0.5 h and accumulated continuously to its peak of 3.863 ng/g at 30 days

Table 2 (continued)

Reference	Compound	Sample settings	Quant. method	Key observations
Langford et al. 2014	Emamectin benzoate	Water, sediment, and biota samples in the vicinity of five aquaculture locations along the Norwegian coast	LC/MS/MS	Remains in the sediments for a considerable period of time The concentration in all of the blue mussel samples collected was below the methods detection limits
Löffler et al. 2005	Ivermectin	Sediment and water: were removed from a sampling site located near to the source of the creek, were filtered and stored	LC-tandem MS	Showed a rapid loss in the system. It moved rapidly from the water compartment into the sediment. This rapid and extensive sorption of ivermectin onto the sediment which is mainly attributable to its lipophilicity
De Steene et al. 2010	Fenbendazole	Surface water, influent or effluent: were collected and filtered	Analyzed in seepage water with solid phase extraction and LC–MS/MS	It was detected in at least one sample at low concentrations and observed in a sample collected near the discharge of a WWTP receiving water from chemopharmaceutical industries and others
Goessens et al. 2020	Ivermectin	Water: were collected with plastic buckets and sieved on spot to eliminate large particles	SPE-UHPLC-MS/MS	Ivermectin were not detected in any of the ponds due to their higher aqueous solubility log p values and high ability to bind to soil
Goessens et al. 2020	Flubendazole	Water: Grab water samples were collected with plastic buckets and sieved on spot to eliminate large particles	There were filtering processes and the use of SPE-UHPLC-MS/MS for identification	Flubendazole were not detected in any of the ponds due to their higher aqueous solubility log p values and high ability to bind to soil
Van De Steene and Lambert 2011	Flubendazole	Surface water: samples were collected from a stream near the laboratory and were filtered and stored at 4 °C until extraction	Electrospray ionization mass spectrometry (ESI–MS)	It was present in several samples analyzed

Table 3 Studies exploring aspects of pollution with veterinary antiparasitics outside the scope of toxicity testing or environmental fate

Reference	Compound	Location	Stated objectives	Methodological information	Key findings
Brooks et al. 2019	Emamectin benzoate	Oslo Fjord (Norway)	To determine the uptake and depuration of drugs by *Mytilus edulis*	Measurement in collected field samples near fish farms Laboratory exposure: 14 days of uptake (exposure) + up to 21 of depuration in clean seawater	Below limit of detection in field samples. Likely persistent in mussel tissue. Kinetic bioconcentration factor (BCF): 49. Calculated elimination half-life (t1/2): 14 days
Liebig et al. 2010	Ivermectin	European Union	(1) To conduct an ERA for the parasiticide ivermectin (2) To show gaps and to propose improvements of the existing guidelines	Criteria: VICH 2000, 2004; EMEA 2008. Species and routes of administration Integration of data from non-standardized studies	Ivermectin is a substance of high concern. Guidance needed for higher-tier or tired studies. ERA for ivermectin needs reassessment

resulted in a relatively large number of entries for non-target organisms tested (75 entries in total) (Fig. 2B). Due to the diversity of test organisms in the included studies, we divided them into approximate biological groups rather than taxonomically solid categories (Table S2). This diverse set of test organisms also yielded a variety of outcomes that ranged from the individual level to the population level (from liver gene expression to community abundance). The level of identification of organisms also varied, with some studies distinguishing between individual species in each genus while others provided only order and phylum level information about the studied organisms (*e.g.*, Nematoda, Cladocera, and Tardigrada). Where provided, we also comprehensively include metrics such as EC_{50} values to compare toxicity between biological groups (Tables S3 and S4).

Invertebrates were the most studied group of organisms, accounting for 70.6% of the total number of entries (Fig. 2B). This category included all animals outside the phylum Chordata. Among them, crustaceans were the most predominant ($n = 27$; 51%), with daphnids appearing most frequently ($n = 9$; 17%), and *Daphnia magna* occupying the position of most studied individual species ($n = 8$; 15%). *D. magna* also proved to be a sensitive test organism, being the most sensitive organism to five of the compounds as well as yielding some of the lowest mean effect concentrations (EC_{50}) in the studies included (Tables S3 and S4).

Overall, the trend of higher toxicity to invertebrates reflects the fact that antiparasitics are intended to target this group. Many active ingredients in antiparasitics, such as pyrethroids and organophosphates, are commonly found in insecticide and pesticide formulations (Akre 2016). Other active ingredients in veterinary antiparasitics include pyrethrins and carbamates (Anadón et al. 2009; Akre 2016), which illustrates how these pharmaceuticals intersect with pesticides in terms of vulnerable non-target organisms. Most importantly, parasiticides, agricultural pesticides, and insecticides are designed to maximize toxicity to specific invertebrate taxa (mostly arthropods and nematodes) and in many cases optimized for conserved structures to allow a broader spectrum of activity (Powell et al. 2018). This "toxicity by design" could be why Kools et al. (2008) and Di Nica et al. (2015) found that antibiotics and parasiticides typically ranked high in their risk-based assessments of veterinary pharmaceuticals.

Accordingly, the retrieved EC_{50} data indicate a trend of higher toxicity toward invertebrates, especially microcrustaceans such as *D. magna*, which was the most sensitive species to four out of the seven compounds (ivermectin, fenbendazole, abamectin, and doramectin) tested in more than one species. In fact, the ubiquity of *D. magna* as a test organism, combined with its low EC_{50}, frequently placed it as the most sensitive species in multi-species studies (Tables 1 and 3). This trend is in line with previous calls for research on veterinary antiparasitics that were primarily concerned with declines in populations of insects and small riverine invertebrates (Powell et al. 2018).

We favored EC_{50} to compare toxicities among non-target organisms because substantially more articles disclosed EC_{50}s than LC_{50}s or NOECs. We also consider that EC_{50} values represent a more sensitive metric compared to LC_{50}, as many chemicals still produce detrimental effects that manifest at the population level without causing mortality. Additionally, only specific effects are required by many standardized protocols, such as the OECD Test No. 211, which tests the reproductive output of *D. magna* in response to chemical exposure (OECD 2018). Despite not being lethal, this is an effect that leads to a reduction in population size.

Prominent examples of this phenomenon of trickling up to detrimental populational outcomes are the disruption of developmental and neuronal processes. Benzimidazoles,

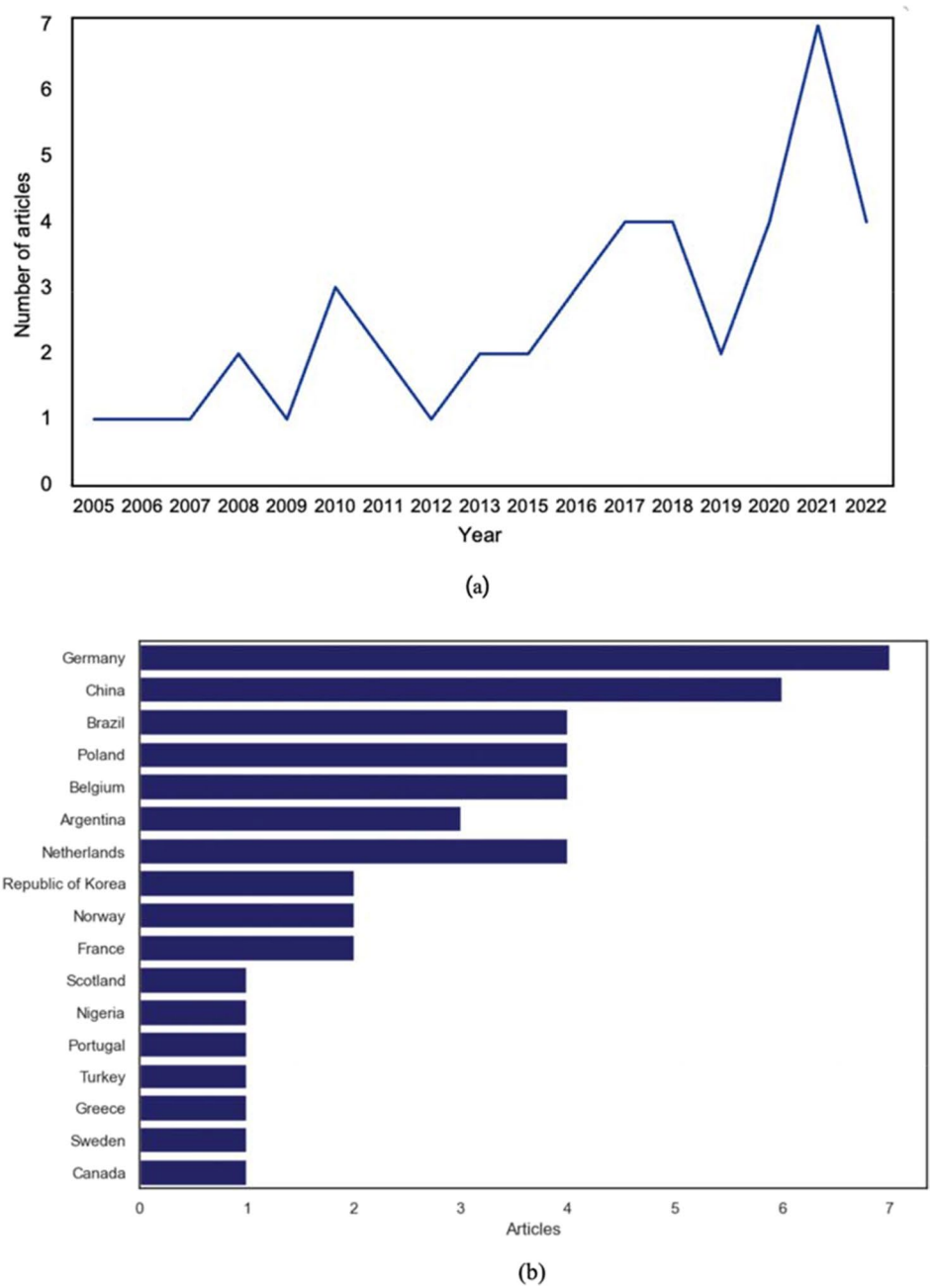
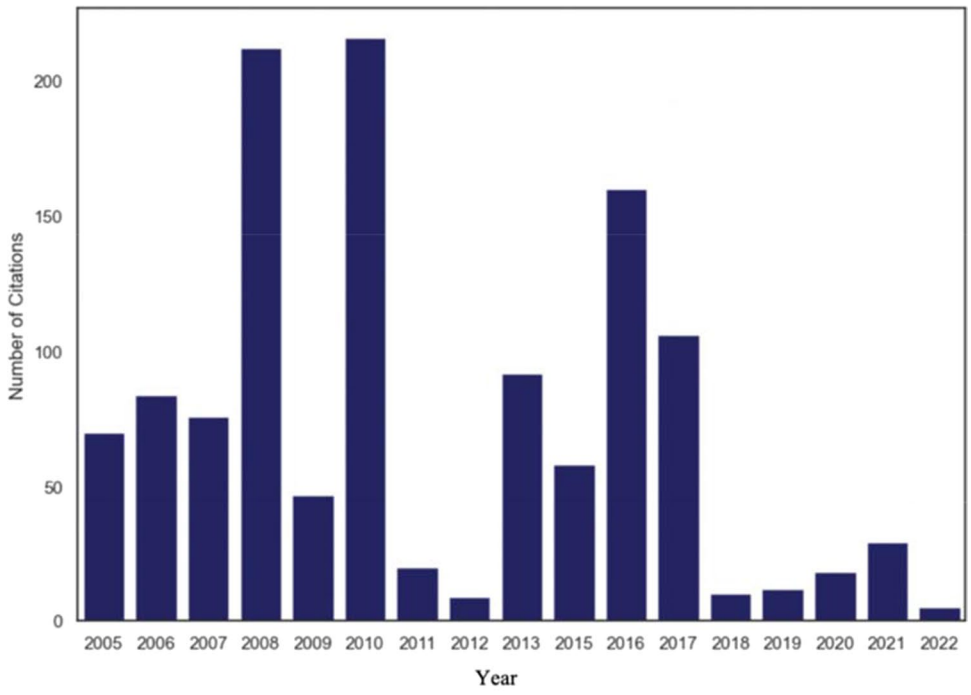


Fig. 1 Bibliometrics data of selected articles. **a** Number of articles × year. **b** Number of articles × Country. **c** Number of citations × year. **d** Impact factor. **e** Absolute and cumulative number of articles over the years

for instance, are beta-tubulin inhibitors that interfere with cell division during early development of zebrafish, causing skeletal deformities and adversely impacting movement (Zhang et al. 2020), which ultimately reduces fitness. This type of sub-lethal drop-in fitness can also be expected for chemicals with neurotoxic effects, as previously reported for MLs (Spinosa et al. 2008; Rosa et al. 2016). Avermectins (ivermectin, abamectin, doramectin) and milbemycins (moxidectin and nemamectin) are two of the main groups of macrocyclic lactones. The main difference between these groups is the presence of the bisoleandrosyloxy substituent at C-13 of avermectins, which is not found in milbemycins. Furthermore, avermectins have a glycosylated lactone backbone, while milbemycins do not. Despite chemical differences, the molecular structures of both groups are superimposable and exert neurotoxic effects on targets, mainly interfering with neurotransmission via GABA (Lumaret et al. 2012).

Other classes of veterinary antiparasitics, such as pyrethroids, pyrethrins, organophosphates, and carbamates, also exert neurotoxic effects from the inhibition of acetylcholinesterase (AChE), which has been documented in several aquatic organisms, including fish, crustaceans, and clams (Toumi et al. 2016; Arora et al. 2017; Singh et al. 2018; Li et al. 2018). At the population level, neurotoxicity at large may lead to behavioral

Fig. 1 (continued)



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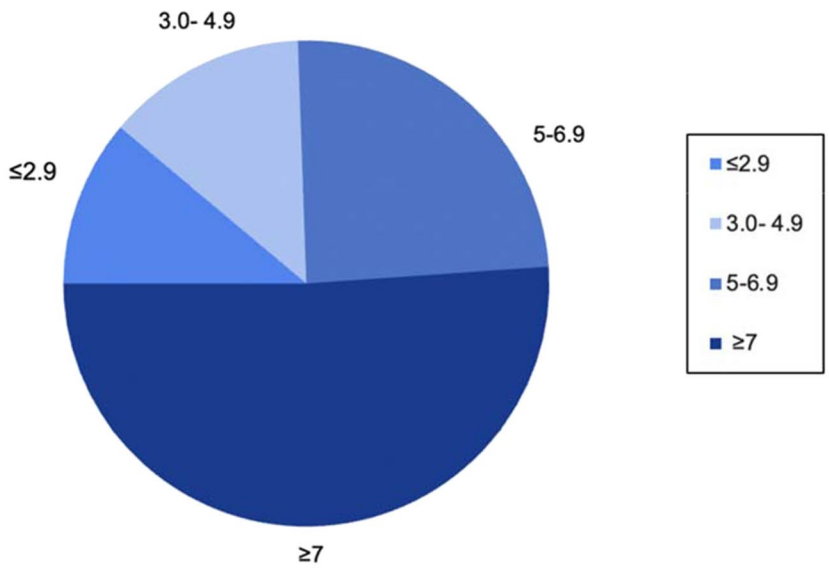

(d)

changes that increase predation or disrupt social behaviors (Sandoval-Herrera et al. 2019; Armstrong et al. 2019; Bedrossiantz et al. 2020; Faria et al. 2020). An aggravating factor for these classes is that they commonly appear as pour-on treatments, which provide a direct track for the compounds to reach nearby ecosystems unchanged (Loeb 2018).

Endpoints and testing conditions

Mode of action (MoA) and toxicity to the target species are not the only variables affecting the ultimate toxicity endpoints observed in a given species. Other factors such as time and length of exposure, chemical properties, experimental conditions, toxicokinetics and toxicodynamics, formation of

Fig. 1 (continued)

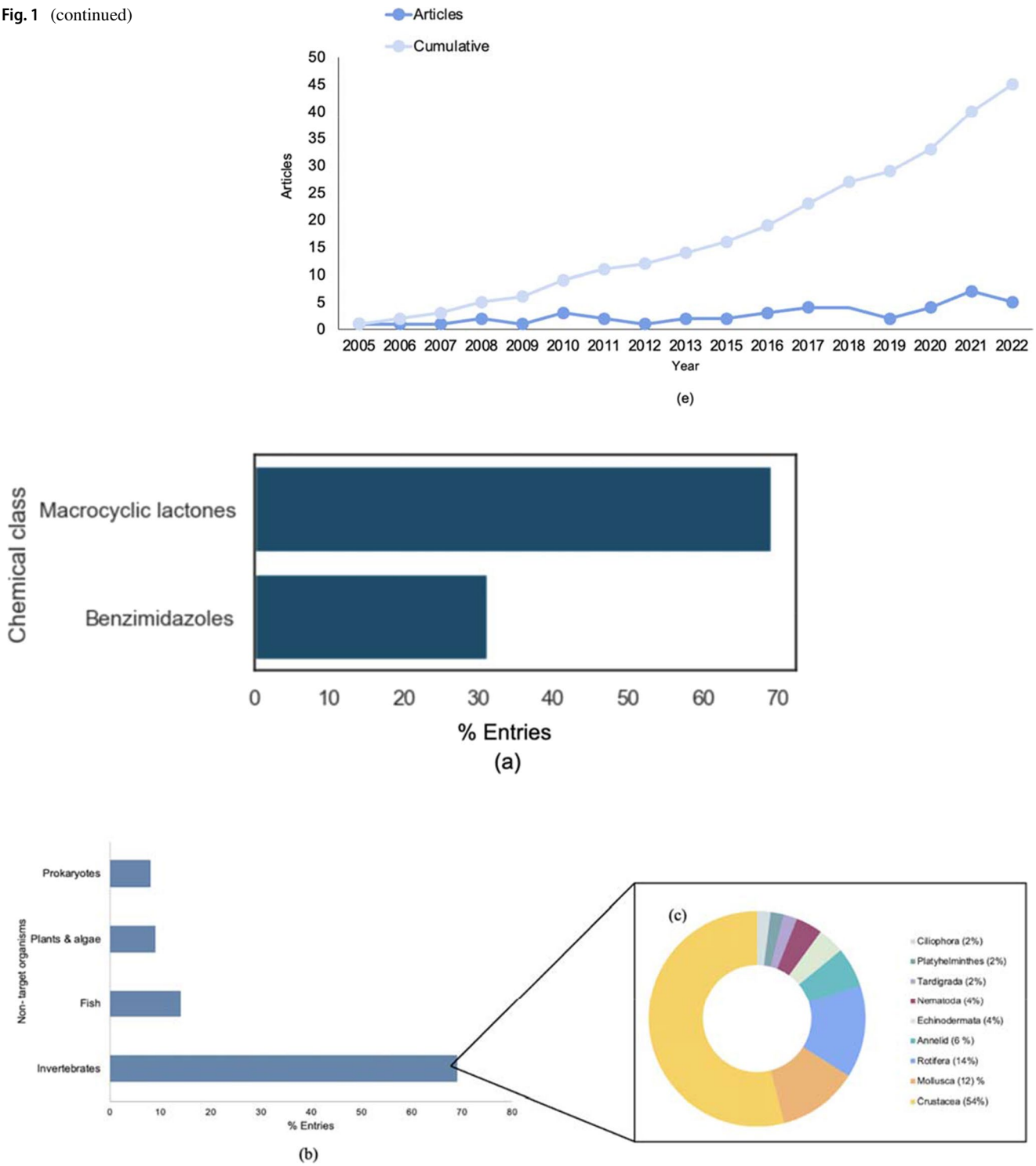

Fig. 2 Frequency (%) of macrocyclic lactones and benzimidazoles tested for toxicity to non-target organisms (**a**); of biological groups used in toxicity assays with veterinary antiparasitics (**b**); of invertebrates within those biological groups **(c)**. In (a) each entry represents a study of one compound within the chemical class on a research article. In (b) and (c) each entry represents a study of the effects of an individual chemical on a single test organism within a research article

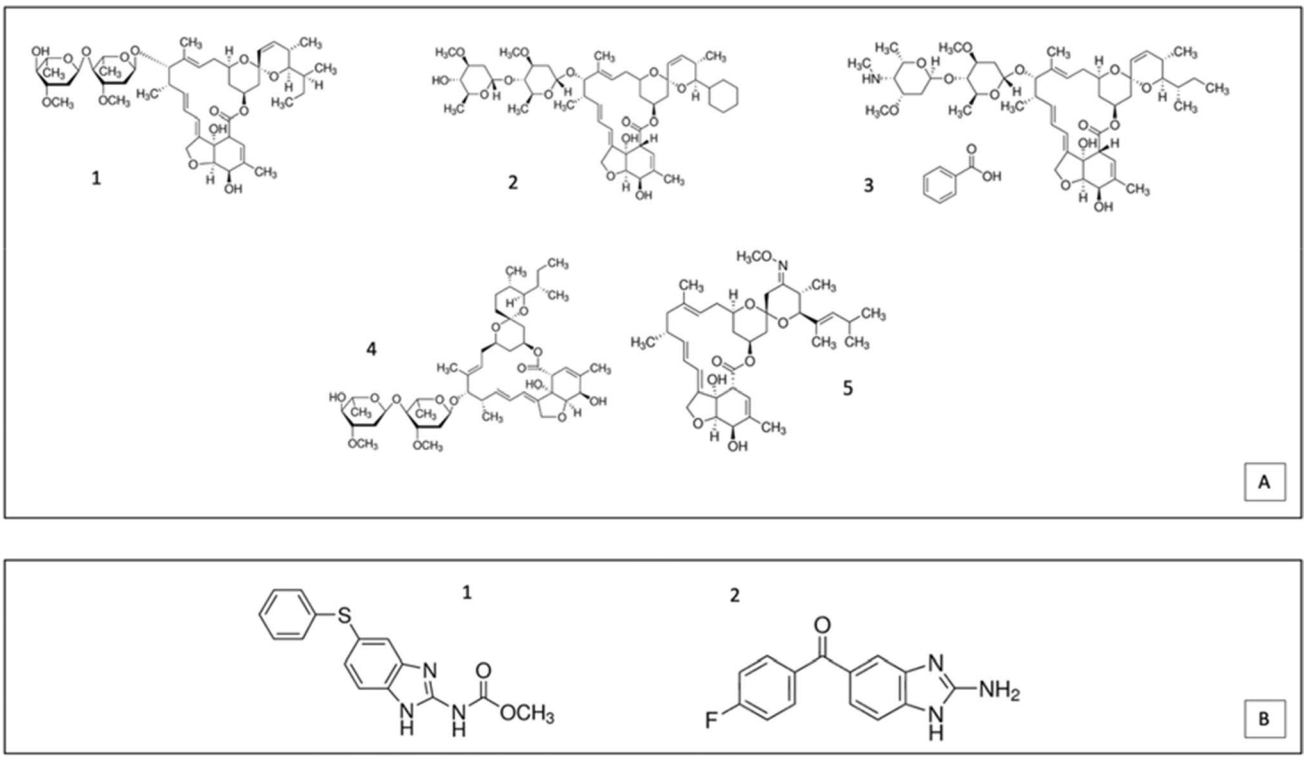

Fig. 3 Molecular structures of the main macrocyclic lactones and benzimidazoles reported in the studies. (**a**) 1, Abamectin; 2, doramectin; 3, emamectin benzoate; 4 = ivermectin; 5 = moxidectin. (**b**) 1, Fenbendazole; 2, flubendazole

derivates in the environment or by biotransformation, and specific biological peculiarities can cause disagreements in the effects between related species and chemicals. In a study with five benzimidazole-based antihelminthics, Oh et al. (2006) found various degrees of toxicity toward *D. magna.* Given that the compounds are structurally similar, the authors argue that the differences can be explained by the octanol–water partition coefficient (K_{ow}) of the chemicals, which is a lipophilicity parameter.

The span and endpoints investigated in individual toxicity investigations also varied greatly, but mostly focused on standardized acute toxicity assays, which is another aspect of the diverse test organisms. For example, the OECD Protocol No. 201 requires a 72-h exposure to assess growth inhibition in alga and cyanobacteria over several generations, while the guidelines for *D. magna* acute toxicity (OECD 2004) require a 48-h exposure. The most reported endpoints for *D. magna* were "immobility and toxicity" (Tisler et al. 2006; Bundschuh et al. 2016). Another common toxicity test was with *Vibrio fischeri*, focusing on the "luminescence inhibition" endpoint (Tisler and Kozuh Erzen 2006; Wagil et al. 2015a, b). Longer-living organisms such as zebrafish require a 96-h exposure to assess acute toxicity toward embryos and 21 days to assess certain endocrine disturbances in sexually mature individuals (OECD 2009, 2013). Endpoints such as "toxicity" and "swimming activity" were widely reported in tests with zebrafish (Tisler and Kozuh Erzen 2006; Santos et al. 2023).

However, for the results to translate into ERA-relevant information, these hypotheses need to be investigated at several levels of biological organization, with tiered methodological approaches. The predominance of strictly laboratory-based tests in accordance with standardized guidelines (*e.g.*, OECD ISO), compared to a smaller number of field and microcosm studies, is consistent with the single ERA paper in our pool (Liebig et al. 2010), which sook to establish a case-study, multi-tiered ERA for ivermectin. As noted by the authors, even though strictly laboratory-based assays provide useful data on non-target toxicity and chemical properties, more information and standardized protocols at higher-tier levels are imperative. Additionally, Di Nica et al. (2015) have documented the lack of chronic toxicity data as another potential source of hinderance.

Environmental fate

Although studies on the environmental fate of emerging contaminants have become increasingly common in recent years, our research data showed that this type of study with MLs and BZs is still proportionately less performed than toxicity tests. Toxicity assessments and the environmental fate of contaminants must go hand in hand in order to

provide the construction of an environmental risk assessment that delineates potential health risks and supports decision-making processes.

Among the MLs, ivermectin was the most detected substance. Ivermectin showed a rapid loss in the system, moving rapidly from the water compartment into the sediment. This rapid and extensive sorption of ivermectin onto the sediment is mainly attributable to its lipophilicity (Löffler et al. 2005; Rath et al. 2016; Wang et al. 2019). This same pattern was reported for doramectin, eprinomectin, moxidectin, and abamectin by Chen et al. (2021). Eprinomectin and emamectin benzoate remain in the sediments for a considerable period of time (Litskas et al. 2013; Langford et al. 2014), while ivermectin and abamectin are rapidly degraded (Dionisio and Rath 2016; Rath et al. 2016).

Flubendazole and fenbendazole were the most common BZs. Both were frequently detected in water samples (De Steene et al. 2010; Van De Steene and Lambert 2011; Wagil et al. 2015a, b; Goessens et al. 2020; Chen et al. 2021), highlighting the high solubility of flubendazole in water and its ability to bind to sediment (Goessens et al. 2020). In addition to these two BZs, Chen et al. (2021) detected in water samples from the Tuojiang River (Sichuan, China) significant amounts of five other antiparasitic agents of the same class. If we put together the high solubility of BZs in water and the constant supply of these chemicals in aquatic environments, it is possible to delimit the potential risk of these chemicals to non-target organisms, especially adverse effects resulting from chronic exposure.

Conclusions

We provide an informative analysis of the toxicity of macrocyclic lactones and benzimidazoles to aquatic wildlife. The results also supported the speculated trend of toxicity toward invertebrates based on EC_{50} and NOEC values. Likewise, the high frequency of invertebrate entries indicates a preference by the authors to use them as test organisms, demonstrating the importance of this biological group for the toxicity testing of antiparasitics. Additionally, these classes of parasiticides have been frequently found in environmental samples, highlighting their high solubility in water and, for some specific compounds, high stability to degradation.

Therefore, our results provided a basis for a discussion covering the toxicity of antiparasitics of major importance to a large variety of test organisms. Given the importance of antiparasitic drugs in animal production systems worldwide, we posit that they warrant coordinated efforts to expand the literature about their environmental impacts. For this purpose, a range of methodological approaches may be necessary to inform prioritization and mitigation efforts. The data collected suggests that major priority should be given to quantifying compounds in environmental samples that can inform the significance of EC_{50} values. Higher-tier studies, chronic exposures, multispecies exposures, micro- and mesocosms, and transgenerational exposures may also provide realistic exposure scenarios that integrate variables related to both fate and toxicity. Additionally, toxicity assessments that include mechanistic and biochemical information (*e.g.*, biomarker assays, bioaccumulation, biomagnification, and trophic transfer) may be valuable in refining the current information about the odds, routes, and impact of these chemicals.

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