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Registry and ecotoxicological data of *Aedes aegypti* control products

Registro e perfil ecotoxicológico de produtos para controle de *Aedes aegypti*

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ABSTRACT

Introduction: Arboviruses transmitted by *Aedes aegypti* have big relevance for public health worldwide, with chemical vector control being an important mitigation strategy. Nevertheless, the intensive use of insecticides is associated with resistance and environmental toxicity. That is why it is essential to develop and regulate new products, effective and sustainable. **Objective:** To describe the requirements for regulation of insecticides and repellents in Brazil, in the light of international guidelines. To present, comparatively, the active ingredients approved in Brazil, United States (USA) and the European Union (EU). Finally, to conduct a survey of ecotoxicological studies from active ingredients used for vector control. **Method:** Narrative review of national and international regulatory instruments, scientific literature, consultation with regulatory agencies and access to ECOTOX Knowledgebase. **Results:** Brazilian requirements are in line with international standards. All insecticides active ingredients available in the USA have a monograph approved in Brazil by the National Health Surveillance Agency; the EU was more restrictive. There are fewer topical repellents available in Brazil and in the EU, compared to the USA. Many of the insecticides approved for vector control pose a risk to non-target organisms. However, we did not identify studies for some of them in the researched database. **Conclusions:** The EU seems to be the most restrictive agency when it comes to registering insecticides. Specific guides on development of innovative products for vector control are needed, as well as greater transparency in research instruments at the Brazilian agency website. This review also reiterates the necessity of more ecotoxicological analysis regarding insecticides, considering their potential environmental hazard.

KEYWORDS: Arboviruses; *Aedes aegypti*; Registry; Insecticides; Toxicity

RESUMO

Introdução: Arboviroses transmitidas pelo *Aedes aegypti* têm grande relevância para a saúde pública, sendo o controle químico do vetor uma importante estratégia de mitigação. Entretanto, o uso intensivo de pesticidas está associado a seleção de insetos resistentes e impacto ambiental. Por isso, é essencial desenvolver e regulamentar novos produtos, eficazes e sustentáveis. **Objetivo:** Descrever os requisitos para regulação de inseticidas e repelentes no Brasil, à luz de orientações internacionais. Comparar os ativos regulamentados no país com os disponíveis nos Estados Unidos (EUA) e União Europeia (UE). Por fim, realizar um levantamento de estudos ecotoxicológicos dos ativos empregados no controle vetorial. **Método:** Revisão narrativa de instrumentos regulatórios nacionais e internacionais, literatura científica, consulta a agências regulatórias e ao ECOTOX *Knowledgebase*. **Resultados:** As normas brasileiras trazem exigências consoantes com as internacionais. Todos os ativos disponíveis nos EUA têm monografia aprovada pela Anvisa; já a UE mostrou-se mais restritiva. Há menos repelentes tópicos disponíveis no Brasil e na UE, comparando-se com EUA. Muitos dos inseticidas aprovados para controle vetorial representam risco para organismos não alvo. Ainda assim, não identificamos quaisquer estudos para alguns dos produtos no banco

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de dados pesquisado. **Conclusões:** A UE mostrou-se a agência mais restritiva com relação ao registro de inseticidas. Existe a necessidade de guias com orientações específicas sobre o desenvolvimento de produtos inovadores para o controle do mosquito, bem como de ferramentas de busca com maior transparência na página da agência brasileira. Finalmente, esta revisão reitera a importância de análises ecotoxicológicas mais abrangentes para os produtos em questão, considerando seu potencial dano ambiental.

PALAVRAS-CHAVE: Arboviroses; *Aedes aegypti*; Registro; Inseticidas; Toxicidade

INTRODUCTION

Arboviruses, such as dengue, zika, chikungunya, and yellow fever are tropical infectious diseases that have a significant impact on public health and have the *Aedes aegypti mosquito*[1,2]as their main vector. In the past two decades, dengue and chikungunya have become the arboviruses of the greatest impact worldwide, due to the increase in cases of transmission. In Brazil, data from 2016 revealed that dengue was the disease of greatest health relevance in the period, affecting approximately 1.5 million people between 2015 and 2016[3]. In 2019, until August, more than 1.4 million cases of the disease were recorded[4].

The treatments available for these arboviruses are still very limited, being restricted to the control of symptoms. Currently, only the yellow fever vaccine is well established[5]. In this context, the most effective ways of mitigating these diseases are the mechanical, biological, and chemical controls of insect vectors[6].

Mechanical control has the main objective of eliminating breeding sites, mainly through basic sanitation actions. Biological control can be implemented using predators or pathogens capable of reducing the vector population or the transmission of the etiologic agents of these diseases. A highlight of biological control is the use of the bacterium *Bacillus thuringienses israelensis* (Bti), which has relevant larvicidal activity[6]. An innovative form of control is the infection of *Ae. aegypti* with bacteria of the genus *Wolbachia*, which reduces the transmission of arboviruses by the mosquito[7].

Another biological control technique involves genetic modifications of the male mosquito. The change is capable of reducing the population of wild mosquitoes, by generating offspring that does not reach adulthood. Although promising, the initiative is still incipient and should be practiced in a complementary way to other aspects of vector control[8].

Chemical control is carried out through the use of insecticides targeting different stages of development of *Ae. aegypti*, most of which are pyrethroids[9]. Environment-repellent and topical compounds are also applied to avoid contact with the vector mosquito[1].

Among the aforementioned alternatives, the most used is chemical control, therefore, insecticides deserve to be highlighted regarding aspects related to their regulation and environmental impact.

The intensive use of pesticides allows the selection, over time, of resistant insects[9,10,11]. An example is the application of temephos, an organophosphate that was used as the only way to control *Ae. aegypti* larvae for more than three decades in Brazil, and today it is not effective against the vector[9]. The recommendation of the World Health Organization (WHO) to reduce the development of resistance to the available insecticides is the combination of products with different mechanisms of action, and that target different stages of development of the mosquito[12].

Insecticides are land-based pollutants, commonly detected in the environment, due to their extensive use not only for vector control involving public health, but also in agricultural production. Organochlorines, such as dichloro-diphenyl-trichloroethane (DDT), despite having been banned in many countries, are the pesticides found in greater concentration in the soil and water due to their slow biodegradability[13,14]. Another environmental damage related to the use of insecticides is related to the effects on non-target organisms, such as aquatic animals, reptiles, amphibians, plants, and pollinators[15]. Not only environmental insecticides but those applied to the skin present a risk to the environment[16]. Assessing the potential damage to non-target organisms, as well as the persistence in the environment, is part of the process of registering a product so that it is safe for human beings, and for the ecosystems where they will be inserted[17]. In this context, it is important to promote the development and regulation of new formulations, that are effective, safe, and sustainable.

Bearing in mind that the rules applied to the registration and analysis of insecticides in the country are sparse in different public agencies, this article brings, in a didactic manner, the regulatory aspects necessary for the registration of insecticides and repellents in Brazil, in the light of the WHO guidelines.

Additionally, a comparative survey of the active ingredients to control *Ae. aegypti* approved in the United States of America - USA (by the *United States Environmental Protection Agency* – EPA), in the European Union – UE (by *European Chemicals Agency* – ECHA), and in Brazil (by the Brazilian Health Surveillance Agency - Anvisa) was performed. Thus, the objective was to understand if possible regulatory divergences regarding the international guidelines can impact product registration. Finally, considering the potential environmental impact of the use of insecticides, we present an overview of the ecotoxicological studies of the active ingredients marketed in the three countries, with a quantitative survey in the ECOTOX Knowledgebase database.

METHOD

An analysis of documents was carried out on the necessary requirements for the registration of insecticides and repellents for the control of *Ae. aegypti* in Brazil, including current Brazilian legislation and WHO recommendations. An overview of the active ingredients registered in the USA and Brazil was also evaluated, since the regulatory frameworks established by Anvisa guide the adoption of WHO or EPA recommendations for product development. The active ingredients available in the EU for vector control were also consulted, comparatively between the three countries.

Bearing in mind that EPA is the only regulatory agency, of the three discussed in this paper, which provides a search system for products approved for specific control of *Aedes*, the active ingredients obtained were based on in its National Pesticide Information Center (NPRO) database. To the result of this research, other ingredients recommended by the WHO and the Centers for Disease Control and Prevention (CDC) for mosquito control were added. Thereafter, it was verified if Anvisa and ECHA authorized these ingredients.

The information related to the products used in Brazil was obtained through official notes from the Anvisa Portal, as well as from the Agency's ombudsman and documents from the Ministry of Health (MS). Those used in the USA were made available by NPRO (environmental insecticides), EPA, and CDC (topical repellents). The active ingredients available in the EU were obtained from data from ECHA (groups PT18 and PT19 which include environment insecticides and repellents) and European Center for Disease Prevention and Control (ECDC).

A quantitative overview of ecotoxicological studies of the active ingredients in aquatic and terrestrial organisms was obtained from consultation with the ecotoxicological database ECOTOX Knowledgebase[18]. Insecticide assets were researched by the Chemical Abstract Service (CAS), or scientific name in the case of organisms. In addition, ecotoxicological studies of insecticides available in the literature were addressed.

RESULTS

WHO recommendations for insecticide registration

According to the WHO, insecticides should be subjected to analyzes of efficacy in the target organism and toxicological analyzes to investigate whether the product is safe for human health, animals, and the environment. Ensuring that registered products are effective and safe is the primary objective of regulatory agencies worldwide. Thus, the company interested in registering the pesticide must present the documents that prove its effectiveness and provide instruments for the regulatory agency to carry out a risk analysis and propose handling requirements for the product and its residues. After analysis, depending on each agency's criteria, the registration request can be granted in full or provisionally, with restrictions or conditions, or be rejected when the product is not effective or safe[17].

The studies presented in the registration dossier must be of high quality, reliability, and, whenever possible, based on standards and protocols of international organizations, such as the Food and Agriculture Organization (FAO) of the United Nations, WHO, and the Organization for Economic Cooperation and Development (OECD). Important information that must be included in the dossier are: (A) identity and physicochemical characteristics of the active ingredient and its respective formulation; (B) analytical methods; (C) human and environmental toxicity; (D) proposed use and labeling; (E) product safety data sheet; (F) proof of effectiveness for the intended use (assessed against the vector and, additionally, under the ecological conditions of the environment in which the product is intended to be applied); (G) waste generated by the use and application of the product; (H) handling of packaging; (I) waste disposal. However, requirements may vary according to the characteristics of the product, such as the nature of the pesticide and its scale of use[17].

There are international guides that establish criteria for studies on the effectiveness of pesticides. In the case of products for the control of disease vectors with an impact on public health, the criteria established by the WHO Pesticide Evaluation Scheme (WHOPES)[19] are used. In addition to proving effectiveness, the company must present information on human and environmental toxicity according to the exposure arising from the form of application and use of the product. Safety studies in humans may include acute oral, dermal, inhalation toxicity; dermal and eye irritation; dermal sensitization; toxicity due to repeated administration (subacute to chronic); reproductive and developmental toxicity; in addition to studies of carcinogenicity, genotoxicity and related to the metabolism of plants and animals[17].

The ecotoxicity profile must be based on toxicity studies on non-target aquatic and terrestrial organisms appropriated to the intended use of the pesticide. Information on persistence and bioaccumulation of the active ingredient and formulation in the environment is also required[17]. There are several protocols made available by the OECD in different non-target organisms for the aforementioned experiments[20].

In view of the great relevance associated with the development of vector resistance, the competent authority should assess the potential risk of resistance development at the time of registration. Therefore, the interested company must make available, for example, cases of resistance already reported for similar compounds[17].

Overview of the use and registry of insecticides and repellents in Brazil

The registration of insecticides in Brazil is supported mainly by three federal institutions: the Ministry of Agriculture, Livestock and Food Supply (MAPA); the Ministry of the Environment (MMA), and the MS. According to Decree No. 4,074, of January 4, 2002[21], it is up to MAPA, MMA, and MS to grant registration of pesticides, technical products, pre-mixtures, and related products. However, each of these institutions is responsible for the technical analysis of product registration requests according to

their expertise. The MS, represented by Anvisa, according to Decree No. 3.029, of April 16, 1999[22], which approves its regulation, is responsible for granting the registration of products intended for use in urban, industrial, household, public or collective, water treatment and use in public health campaigns, as is the case with insecticides used to control *Ae. aegypti*[21]. The MMA carries out the environmental assessment of registered public health products and establishes their dangerousness. In this case, MAPA does not participate in the registry.[21]. Among Anvisa's duties is also the registration of insect repellents for application on the skin, which are classified as cosmetic products by the institution[23].

Registry of environmental insecticides in Brazil

Sanitizing products for the control of vectors related to public health must be registered in accordance with the requirements of Resolutions of the Collegiate Board (RDC) No. 34, of August 16, 2010[24] and No. 59, of December 17, 2010[25], by Anvisa. This category includes environmental insecticidal products, also called environmental repellents by the agency[26].

Sanitizing products can have three functions, according to definitions in RDC No. 59/2010, which establishes the procedures and technical requirements for the notification and registration of sanitizing products: (I) disinfection, (II) disinfestation, or (III) deodorization. Based on the definitions, insecticides are classified as disinfestants - which kill, inactivate, or repel unwanted organisms in the environment, on objects, inanimate surfaces, or on plants[25].

According to the aforementioned resolution, disinfestants are classified as risk II and, therefore, must be registered with Anvisa. The technical report of the product, submitted for registration, must contain: category (insecticide or repellent), destination/application, qualitative and quantitative composition, denomination and chemical characteristics, mode of action, packaging, batch identification system, methodology of analysis of the active ingredient, degree of purity of the ingredients, identity/concentration/toxicity of the impurities, mode and restrictions of use, form of presentation, physicochemical incompatibilities, pests against which it is indicated, toxicological data, risk assessment, efficiency studies, stability studies, as well as the final destination of the product[25]. The acceptable toxicity limits are described in Resolution No. 34/2010[24], in accordance with the WHO provisions[27].

According to Anvisa, in disinfestant products, only the use of active ingredients that have monographs approved by the agency is allowed. In the case of a previously unauthorized active ingredient, that is, of an innovative character in the country, one of the initial measures for registration is the presentation of toxicological data provided in Appendix IV of Resolution No. 34/2010[24] which, upon approval, will culminate in the publication of the monograph on the agency portal[28]. The monograph presents, in addition to toxicological data, the common and chemical name of the active ingredient, class, indication of use, and maximum residue limits[29].

The WHO recommends six insecticides, approved in the scope of public health, to be used in the control of adult vector mosquitoes. Of these, five belong to the class of pyrethroids - deltamethrin, lambda-cyhalothrin, permethrin, allethrin, cyphenothrin - and the other is malathion (organophosphate)[30]. Most of the registered insecticides are based on pyrethrins or pyrethroids[26]. However, malathion has been used as an insecticide to control adults, due to the resistance presented by the vector to pyrethroids in the country[31,32]. Among the larvicides used are: pyriproxyfen[33], methoprene[29], neem oil (azadirachtin)[29,34], diflubenzuron[33], novaluron[35], Bti[32], and spinosad[36].

Registry of topical repellents in Brazil

Topically applied insect repellents are classified, for registration purposes, as cosmetic products and must comply with the technical requirements of RDC No. 19, of April 10, 2013[23]. According to this resolution, in order to register insect repellents, they must be proven to be safe and effective. Data should include primary and accumulated skin irritation, skin sensitization, and photosensitization. For effectiveness, the guidelines stipulated by EPA, WHO, or other internationally recognized methodologies must be used[22,37].

The WHO protocol on the evaluation of the effectiveness of repellents used on the skin establishes that, initially in laboratory tests, the effective dose and the protection time provided by the product under evaluation are determined. At this stage, the dose-response curve is determined, in addition to the doses responsible for 50.00% and 99.90% of the effect. As a positive control, N,N-diethyl-meta-toluamide (DEET)[38] is used.

In Brazil, there are repellents sold with DEET, icaridin, IR3535, and citronella oil that are effective against *Ae. aegypti*, according to an alert by Anvisa No. 3,032 on the use of repellents and application of insecticides[26] and questioning via the Agency's ombudsman[39]. DEET is the most widely used repellent in the world, with an excellent safety profile. In the zika virus protection guides, DEET has been the repellent of choice, even for pregnant women[40,41].

Overview of the registry of environmental insecticides and topical repellents in the USA

According to EPA, to date, there are eight different active ingredients registered in the US as topical repellents against mosquitoes. Among them are the oil of *Nepeta cataria* - catmint (four products); citronella oil (four products); DEET (more than 500 products); IR3535 (45 products); lemon eucalyptus oil (13 products); para-menthane-diol (PMD) (eight products); icaridin (40 products); and 2-undecanone (one product)[41,42,43]. The CDC recommends that DEET, icaridin, IR3535, lemon eucalyptus oil, PMD (synthetic form of lemon eucalyptus oil), or 2-undecanone to be used for specific protection against the *Ae. aegypti*[44].

As larvicides Bti, diflubenzuron, spinosad, methoprene, novaluron, and pyriproxyfen are used, in addition to films and oils placed on the water surface, capable of preventing gas exchange

between atmosphere and the aquatic environment[37]. However, in the NPRO, only the active ingredients Bti, methoprene, and pyriproxyfen were found with a specific indication for control of the *Ae. aegypti*[45], although all other ingredients cited by the CDC[46] are registered with the American agency[45].

In research for pesticides used to control *Ae. aegypti* in NPRO, 80 active products were found, mostly consisting of pyrethrins and pyrethroids. Among the active ingredients listed are: permethrin, prallethrin, phenothrin, metofluthrin, esfenvalerate, pyriproxyfen, lambda-cyhalothrin, methoprene, and the fungus *Beauveria bassiana*[38]. The pyrethroids allethrin and cyphenothrin, and the organophosphate malathion, recommended by the WHO for adult control[30], are registered by EPA but not with a specific indication for *Ae. aegypti*, in consultation with the NPRO[45].

Overview of registry of environmental insecticides and topical repellents in the EU

Products intended for the protection of humans, animals, materials, or articles against organisms such as pests or bacteria are referred to as biocides by the EU. The registry of these products is described by the regulation Biocidal Products Regulation (BPR, Regulation (EU) 528/2012). The active substances present in biocides must, as a general rule, be previously approved by ECHA[47]. The active substances approved by the agency for mosquito control can be classified as (PT18) insecticides, acaricides, and products for the control of other arthropods, or (PT19) repellents and attractants. Considering these two groups, there are 88 EU-approved active substances[48]. However, of these assets, it is not possible to measure by the search system how many are indicated for the specific control of mosquitoes.

Of the insecticides used to control *Ae. aegypti* (Chart), four are not approved by the EU (ECHA): esfenvalerate, which had its authorization discontinued, novaluron, malathion, and *Beauveria bassiana*. Allethrin is under analysis by the agency[49].

With regard to topical repellents, ECDC indicates that the CDC's guidelines on repellents for protection against bites by *Ae. aegypti* are followed[49]. DEET, IR3535, and 2-undecanone are approved in the EU, while PMD, lemon eucalyptus oil, and icaridin are under evaluation by ECHA[48].

Ecotoxicological studies of the active ingredients present in products to control *Ae. aegypti*

Pesticides are developed to protect food and/or health. However, its mechanisms of action involve killing, repelling, preventing, or threatening insects, which inevitably presents some toxicity to the environment[50]. Aquatic ecosystems, being the final deposit of waste, are directly contaminated. Models for assessing acute and chronic toxicity of pesticides in these ecosystems involve organisms of different trophic levels, involving microcrustaceans, such as *Daphnia magna, Ceriodaphnia dubia*, *Artemia salina*, and *Dendrocephalus brasiliensis*; fishes, such as *Xiphophorus maculatus* e *Danio rerio* (zebrafish); and crustaceans, such as *Eurytemora affinis* and *Leander tenuicornis*[51,52,53,54].

The ecotoxicological effects can also be evaluated in plants, through phytotoxicity studies, and in animals that interact directly

Chart. Environmental insecticides used to control *Ae. aegypti* (Brazil, USA, EU).

Chemical Abstract Service	Active ingredient	States Environmental Protection Agency	Brazilian National Health Surveillance Agency	European Chemicals Agency
584-79-2	allethrin[a]	authorized	authorized	under analysis
63428-82-0	*Beauveria bassiana*[b]	authorized	authorized	there is no record
NA[c]	Bti[c,d]	authorized	authorized	authorized
39515-40-7	cyphenothrin[a]	authorized	authorized	authorized
35367-38-5	diflubenzuron[c,d]	authorized	authorized	authorized
66230-04-4	esfenvalerate[b]	authorized	authorized	discontinued
168316-95-8	spinosad[c]	authorized	authorized	authorized
26002-80-2	phenothrin[b]	authorized	authorized	authorized
91465-08-6	lambda-cyhalothrin[a,b]	authorized	authorized	authorized
121-75-5	malathion[a]	authorized	authorized	there is no record
240494-70-6	metofluthrin[b]	authorized	authorized	authorized
40596-69-8	methoprene[b,c]	authorized	authorized	authorized
116714-46-6	novaluron[c,d]	authorized	authorized	there is no record
11141-17-6	neem oil (azadirachtin)[d]	authorized	authorized	authorized
52645-53-1	permethrin[a,b]	authorized	authorized	authorized
8003-34-7	pyrethrins and pyrethroids[b]	authorized	authorized	authorized
95737-68-1	pyriproxyfen[b,c,d]	authorized	authorized	authorized
23031-36-9	prallethrin[a,b]	authorized	authorized	authorized

Source: World Health Organization[26]; *Environmental Protection Agency* (EPA)[41]; *Centers for Disease Control and Prevention* (CDC)[42]; European Centre for Disease Prevention and Control (ECDC)[49]; Brazilian National Agency of Health Surveillance[28,29,30,31].
[a] Nominated by the World Health Organization[26]; [b] Registered in the *Environmental Protection Agency* (EPA)[41]; [c] Nominated by the *Centers for Disease Control and Prevention* (CDC)[42]; [d] Nominated by the Brazilian National Agency of Health Surveillance[28,29,30,31]; NA: not applicable; Bti: *Bacillus thuringienses israelensis*.

with plants, such as pollinators[50]. This set of studies is used both to assess the ecotoxicological risk of a given product and to redefine effective and environmentally safe doses to be applied[51].

The presence of insecticide residues has already been detected in soils and sediments in different regions of the world[50], as well as in aquatic environments, where it has already been observed that variations in the pH of the water can directly influence the dissipation of insecticides[55].

Studies with pyriproxyfen, an active agent commonly used in products to control *Ae. aegypti* larvae, indicate toxic effects for some microcrustaceans[51], fishes, and crustaceans[52,56]. Diflubenzuron, widely used to replace temephos due to its resistance, showed high toxicity for *Daphnia magna*[57]. Both diflubenzuron and temephos were considered toxic for fish *Oreochromis niloticus* and *Hyphessobrycon eques*[58]. Another study noted that temephos and diflubenzuron reduced populations of aquatic insects[59]. Synthetic pyrethroids, used to control adult mosquitoes, despite being considered of low toxicity for mammals, showed high toxicity for fishes, shrimps, and lobsters[60,61]. Organophosphates and carbamates, which are said to be less persistent in the environment and less toxic to mammals than organochlorines, affect the reproduction of *D. magna*, as well as the behavior of reptiles[62].

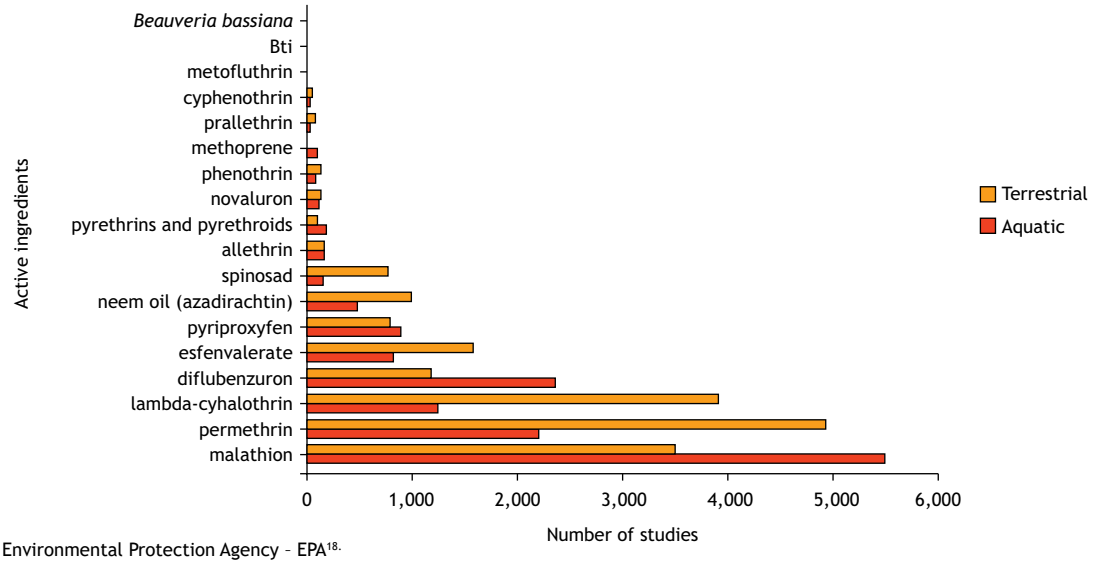
Although studies on amphibians are quite scarce, it was observed that DDT is accumulated in *Xenopus* sp. However, the potential for other pesticides to accumulate in frogs is unknown. Malathion and some pyrethroids were found to have toxicity for this model[15]. One study considered methoprene and Bti as low-risk insecticides for non-target organisms based on the concentrations detected in the environment[63]. However, an EU alert pointed out risks to birds after repeated application of Bti[64].

DEET, a topical repellent used for more than 30 years and considered safe for the general population, has already been reported in water treatment plants and at sea. Despite this, acute and chronic toxicity in aquatic organisms is unlikely, based on the concentrations found in the environment[65].

Mammals are also secondarily affected by insecticides, due to their physiological similarity to insects. Considering that the mechanism of action of these products generally affects the insect nervous system, such as nicotinic acetylcholine receptors, acetylcholinesterase, gamma-aminobutyric acid (GABA) receptors, and voltage-dependent sodium channels, the mammalian nervous system can also be affected[66].

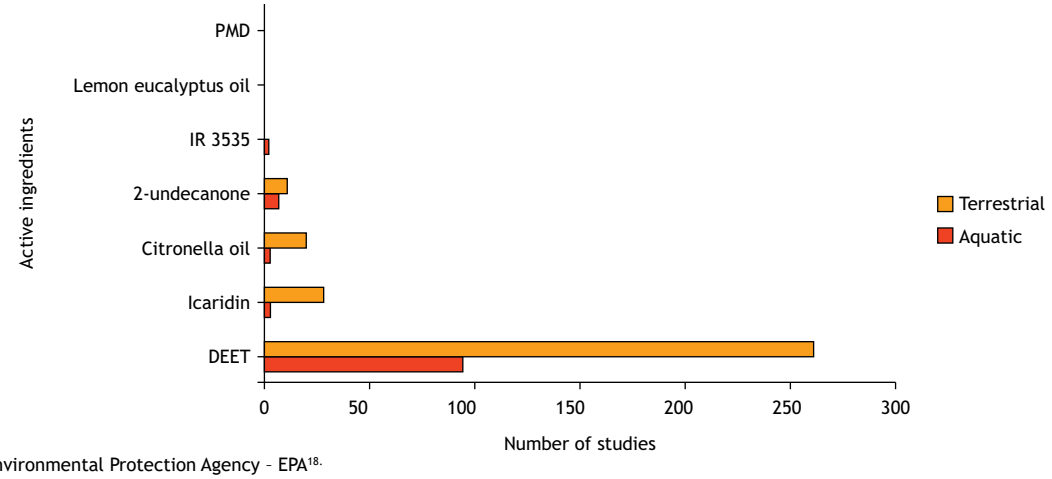
Considering that the exposed data ratify the need to evaluate the environmental risk in non-target organisms associated with the use of insecticides, a quantitative survey of the ecotoxicological studies available in the ECOTOX Knowledgebase database was carried out for these products. 32,717 studies were found for environmental insecticide ingredients (Figure 1), with 14,354 in aquatic organisms and 18,363 in terrestrial organisms. Of the 18 ingredients surveyed, eight are pyrethrins or pyrethroids (allethrin, cyphenothrin, phenothrin, lambda-cyhalothrin, metofluthrin, permethrin, prallethrin, pyrethrins, and pyrethroids). Approximately 41.00% of the ecotoxicological studies found are related to these classes of products, with metofluthrin being the active ingredient with the smallest number of studies available in the class, approximately 0.01% of the total of studies. Two ingredients, Bti and *Beauveria bassiana*, have no ecotoxicological study in the database. The proportion of studies in aquatic and terrestrial organisms proved to be balanced, 44.00% and 56.00%, respectively[18].

The number of toxicological studies for topical repellents is significantly lower (Figure 2), with a maximum of 357 per active ingredient, in this case, DEET. A total of 438 studies were found for seven compounds used as topical repellents, considering investigations in non-target terrestrial and aquatic organisms[18].



Source: US Environmental Protection Agency – EPA[18].
Bti: *Bacillus thuringienses israelensis*.

Figure 1. Ecotoxicological studies on non-target organisms available in ECOTOX Knowledgebase by active ingredient in environmental insecticides.



Source: US Environmental Protection Agency – EPA[18].
PMD: para-menthane-diol; DEET: N,N-diethyl-meta-toluamide

Figure 2. Ecotoxicological studies on non-target organisms available in ECOTOX Knowledgebase by active ingredient in topical repellents.

DISCUSSION

The registry of environmental insecticides and topical repellents is under the responsibility of Anvisa in Brazil, with an environmental hazard analysis carried out by Ibama[21,23,24,25]. The resolutions established by Anvisa are in accordance with the WHO pesticide registry guidelines[17], including the acceptable toxicity limits[17,24].

The vast majority of environmental insecticide products registered in the USA are based on pyrethroids, as well as in Brazil. As a consequence of this limitation of active ingredients available for vector control, the rapid and sparse development of resistance by insects is observed. The Chart provides a comparative overview of environmental insecticides for the control of *Ae. aegypti* used in the regions highlighted in this work. All active ingredients present in products approved by EPA for environmental control of *Ae. aegypti*, as well as those indicated by the WHO[30] and by the CDC[46], have a monograph approved by Anvisa. It is inferred, therefore, that the evaluation criteria for registering these active ingredients in the two countries, USA and Brazil, are aligned. Neem oil (azadirachtin) is indicated by Anvisa to control the vector, despite not being in the recommendations of these international institutions[30,46]. However, this ingredient is registered with EPA[45] and ECHA[48] agencies; in EPA without explicit indication against *Ae. aegypti*. The EU, on the other hand, was more restrictive regarding the authorization of insecticides. Four assets authorized in the USA and Brazil are not authorized by ECHA.

Although the active ingredients of insecticides have monographs approved by Anvisa, this does not guarantee that there are products marketed with them. For the registry of new products in Brazil, it is necessary for companies to file requests with Anvisa, since the agency does not play an active role in this regard. With the monograph approved for the active ingredient, the company can file the registry request for the product containing that asset, along with the other requirements required by law.

Regarding topical repellents, all those indicated by the CDC[44] are authorized by the American agency[43], whereas in Brazil, three are not included in Anvisa's indications and, in the EU, three are still under review for registry[48]. Citronella oil, although indicated in Anvisa's warning[26], is not guided by the CDC as a form of protection against *Ae. aegypti*[44]. The CDC indicates three other ingredients for protection against vector bites, which are not included in Anvisa's guidelines: lemon eucalyptus oil, PMD, and 2-undecanone[44]. A greater divergence was observed regarding the indication of topical repellents by the agencies and CDC, comparing with data obtained for environmental insecticides.

Considering the active ingredients approved by the three agencies, both for environmental and topical use, the American has the highest number of registered assets, followed by Anvisa and ECHA. This difference suggests that the European agency has stricter registry criteria.

It is important to highlight that the differences between the search systems of the regulatory agencies' web pages resulted in limitations for the present study. Anvisa's portal does not have search engines for products (insecticides and repellents) registered by active ingredient or indication of use. Therefore, it is inferred that the number of registered active ingredients available in this study may be underestimated, considering that it was based on official information on the agency's website and questions via the ombudsman. ECHA, despite offering a search for active ingredients and an indication of use, does not inform the organism against which the substance has been approved.

Regarding the environmental toxicity of insecticides used to control *Ae. aegypti*, it was observed that the availability of studies in the literature, in general, refers to products of environmental application, such as larvicides and adulticides. This finding was reinforced by data obtained from ECOTOX Knowledgebase, in which the absolute number of studies for topical repellents is

significantly lower than those available for environmental insecticides. It is important to reinforce that the products applied to the skin directly reach effluents, through bath water or spatial residues from the application that reach the soil, which may affect several non-target organisms along this path. DEET, which is the most used of topical products, was considered of low environmental risk, due to its biodegradability and the low levels found in aquatic environments. However, these are products subjected to biotransformation and bioaccumulation and may cause toxicity to non-target organisms[16].

It was observed that many of the environmental insecticides used in vector control were detected in soils and water, in addition to being related to acute and chronic toxicity in different non-target organisms. There are few ecotoxicity assessments involving animals of different trophic levels for the same active ingredient. Recent studies concern about the residuality of larvicidal products in the development phase[67], a factor that should be analyzed in parallel with the chronic exposure of organisms present in the application sites.

There is a need for more complex assessments to determine the environmental risk of these products, so that it is possible to reach conclusions that culminate, for example, in changing usage patterns when pesticides threaten the environment. However, there is no clear definition in the national and international standards consulted about which studies would be sufficient to prove environmental safety. It is suggested that the types of tests required for the registry are not specified due to the existence of different classes of insecticides, with their own mechanisms of action and mode of use. Thus, the agency that receives the registry request is responsible for assessing whether the studies presented are sufficient to guarantee the product's safe use.

The environmental risks presented by some of the active ingredients emphasize the need for further ecotoxicological assessments, especially for active ingredients that do not have any studies in the researched database, such as Bti. This larvicide even presents divergent positions on environmental safety in the literature. Methoprene and novaluron also drew attention due to the low number of studies, 114 (0.30%) and 244 (0.70%), respectively (Figure 1), despite having already been associated with risks for some non-target organisms.

CONCLUSIONS

This paper presents a review of the requirements for the registry of insecticides and repellents in Brazil, addressing WHO guidelines. In this regard, it was concluded that Brazilian standards are in line with international requirements. However, there are no specific guides on the registry of innovative insecticides in the country, although monographs of new active ingredients with specific requirements need to be approved prior to the registry of products containing them.

Regarding the comparative analysis of the active ingredients available in Brazil, the USA, and the EU, ECHA (EU) proved to be the most restrictive agency regarding the authorization of insecticides and repellents. The way of obtaining the data varied according to the search tools provided by the agencies, which is a limitation of the study.

Finally, the article shows the need for more comprehensive ecotoxicological studies, which include different non-target organisms for all insecticides used in vector control. It was observed that most insecticides have a certain toxicity for the ecosystems in which they are inserted. Even so, some of the active ingredients marketed do not have ecotoxicological studies or there are few available in the researched database (ECOTOX Knowledgebase). It should be noted that, although comprehensive, ECOTOX Knowledgebase has some limitations. It is likely that not all studies performed are available in this database. Therefore, the failure to identify ecotoxicological studies does not mean that these have not been carried out, despite the fact that this finding warns of the need for greater access to information or studies. In addition, no search tools for this type of information were identified on the Anvisa website. Access to environmental impact data can give consumers the autonomy to choose products that are less harmful to the environment.

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Author's Contributions

Magalhães NMG - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. Silva RL - Planning (study design), data interpretation, and writing of the work. Espindola LS - Data interpretation and writing of the work. All authors approved the final version of the work.

Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.