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Reflection paper on the environmental risk assessment of ectoparasiticidal veterinary medicinal products used in cats and dogs

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1. Introduction

The availability and the use of ectoparasiticidal veterinary medicinal products (VMPs) for companion animals are without doubt an indispensable part of an overall concept to protect public and animal health from ectoparasites and associated diseases as well as to ensure animal welfare. In the last decades, much effort has been invested in the development of suitable active substances and well-adapted products to improve user and animal safety as well as the efficacy of ectoparasiticidal VMPs for cats and dogs. At the same time, research into the environmental safety of such products has been neglected, in spite of their evident insecticidal and acaricidal effects, mainly due to the assumption that the treatment of pets only leads to negligible environmental exposure (see below for details).

In the European Union (EU) and European Economic Area (EEA), the environmental risk assessment (ERA) of veterinary medicinal products is tier-based and conducted in two phases, in line with the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guideline (GL) 6 (EMA, 2000) and VICH GL 38 (EMA, 2004) for phase I and phase II, respectively. Phase I mainly consists of a decision tree focusing on qualitative and quantitative criteria to determine whether the ERA for a VMP for which a marketing authorisation is applied for should progress to a higher tier assessment (i.e. phase II) or if it can end at the first phase. A phase I assessment for VMPs intended to be used in companion animals typically does not require the provision of any information on fate, behaviour and effects of an (active) substance, as the overall conclusion is mostly based on exposure considerations only.

Since the inception and coming into force of VICH GL 6 in 1996 and 2000, respectively, the environmental exposure resulting from the use of VMPs in companion animals has been and still is being considered negligible based on the assumption that, generally, non-food-producing animals are not intensively reared and that thus the application of VMPs to these animals can be considered as an "individual treatment" (see VICH GL 6 question 3 for details). The approval of VMPs for use in non-food-producing animals is thus assumed to be associated with a lower risk for the environment when compared to VMPs for food-producing species simply because there are less animals treated and therefore less total amount of product used (EMA, 2000). Consequently, to this day, VMPs intended for use in cats and dogs and other non-food-producing animals usually do not require the performance of a phase II ERA, regardless of the actual dose applied to the animals (i.e. environmental exposure), such that about two thirds of all products authorised until 2020 did not progress to a phase II ERA solely because of the fact that they were intended for use in companion animals (Fabrega and Carapeto, 2020). That being said, VICH GL 6 provides for the possibility to trigger the so-called "*however clause*", which states that, for some VMPs for which the ERA might otherwise stop in phase I, additional environmental information may be required to address particular concerns associated with their activity and use. However, at least for centrally authorised products, this provision has never been triggered for VMPs for companion animals.

Nonetheless, the subsequently published CVMP GL in support of VICH GL 6 and GL 38 (EMA/CVMP/ERA/418282/2005; EMA, 2016), which has been in force since 2009 and complements both ERA-related VICH GLs with practical guidance on how to perform certain assessment steps, considers specific risk mitigation measures (RMMs) that should be incorporated into the product information (PI) of specific ectoparasiticidal VMPs used in dogs, as described later in this document.

Insects serve essential roles in the food webs of terrestrial and aquatic ecosystems. Major losses of insect diversity as well as biomass in Europe and around the globe that have been documented in a spate of high-profile reports are therefore of major concern (D. L. Wagner, 2020). Along with habitat loss due to intensive agriculture and urbanisation, environmental pollution, including that by synthetic pesticides, appears to be a major driver for this observed species decline (Sánchez-bayo and

Wyckhuys, 2019). At the time the concept for this reflection paper was developed, several publications attributed, at least to some extent, the presence of ectoparasiticidal substances such as neonicotinoids (e.g. imidacloprid) and phenylpyrazoles (e.g. fipronil) in wastewater treatment effluents and in urban surface run-off to the use of ectoparasiticidal VMPs for pets (Sadaria *et al.*, 2017; Teerlink *et al.*, 2017; Cryder *et al.*, 2019; STOWA, 2019). Furthermore, Little *et al.* (2020) recommend the need to revisit the current approach of considering the exposure from ectoparasiticidal VMPs used in companion animals as being negligible. This view is supported by well-established knowledge on the toxicity of ectoparasiticides towards aquatic organisms, with many having very low predicted no effect concentrations (PNECs) (EFSA, 2013a, 2014). In addition, a potential link between the death of songbird chicks and the treatment of dogs with parasiticidal VMPs was highlighted in another recent publication (Guldemond *et al.*, 2019).

It is acknowledged that some of the cited articles and the respective conclusions are controversially discussed, for instance in publications by (Cauvin, 2020; Loeb, 2020b, 2020a; Murphy and Wright, 2020b, 2020a; Shotton, 2020; Tarr, 2020; Whitehead and Goulson, 2020), and that many potential sources other than VMPs for companion animals are known to contribute to concentrations of ectoparasiticidal active substances measured in the environment. Furthermore, at the time the concept paper preceding the present reflection paper (RP) was published (EMA, 2020), available monitoring data originated to a large extent from studies performed outside of the EU/EEA, with different regulatory frameworks and different product formulations for such VMPs, which may not be representative for the situation within the Union. Because of the above-mentioned uncertainties, the data situation called for a more in-depth evaluation.

In the meantime, numerous additional publications, including peer-reviewed reports and data from studies performed in Europe, e.g. (Anthe *et al.*, 2020; Domingo-Echaburu *et al.*, 2021; Perkins, Whitehead, Civil, *et al.*, 2021), which also address the above-mentioned concerns and which will be discussed later in this RP, have been published. Moreover, parasiticides in general represent the second largest segment of the global animal health market with the global market share for parasiticides intended for use in companion animals exceeding that for livestock, and a total share of 49% and 23% are attributable to ectoparasiticides and endectocides, respectively (Selzer and Epe, 2021).

Therefore, and against the background of the EU "Strategic Approach to Pharmaceuticals in the Environment" (EC, 2019), which highlights the importance to "[…] identify the pharmaceuticals that pose a risk through their individual presence in the environment, so that risk management efforts can be targeted", as well as Article 73(2)(c) of the Regulation (EU) 2019/6, which states that the reporting of suspected adverse events including "[...] any environmental incidents observed following the administration of a veterinary medicinal product to an animal [...]" should be encouraged, the CVMP decided to publish the present RP.

2. Aims and scope

2.1. Problem statement

Ectoparasiticidal VMPs intended for use in cats and dogs have an insecticidal and acaricidal activity that could impact free-living non-target insects and mites and thus impact ecosystems. VICH GL 6 (EMA, 2000), which is currently applied in the frame of the marketing authorisation process of such VMPs considers these risks to be negligible due to the small quantities used on each individual animal. However, due to an increase in companion animal populations as well as changes in the management thereof, this assumption may not be appropriate anymore.

2.2. Aims

This document has been developed to communicate the CVMP's view on the current state of the scientific discussion on the potential environmental impact(s) of the use of ectoparasiticidal VMPs used in companion animals, and to provide an opportunity for discussion and clarification in this fast-evolving scientific field in which experience is limited.

Therefore, this reflection paper aims to:

- give an overview on the current situation in the EU/EEA regarding the use of ectoparasiticidal VMPs for companion animals and the active substances contained therein,
- identify whether the current approach for the ERA of VMPs used in cats and dogs containing (ecto-)parasiticidal substances remains scientifically justified,
- evaluate the amounts and potential routes of environmental exposure, including an estimation of the environmental risks resulting from the use of ectoparasiticidal VMPs in companion animals,
- explore the need for and applicability of additional RMMs for such products, and
- reflect on possible monitoring options that could be considered for relevant substances.

2.3. Scope

As the ERA of ectoparasiticidal VMPs used in companion animals is a wide-ranging topic, the CVMP decided to adopt a pragmatic approach and limit the scope of the present reflection paper as shown in **Table 1**, in order to achieve the objectives defined above. The examples given for topics, which are outside of the scope of the present reflection paper, are only illustrative and non-exhaustive.

Table 1. VMPs and active substances within the scope of the present reflection paper

Parameter	Scope
Target species	Cats and dogs *Not within the scope are other companion animals such as horses, rodents and rabbits.*
Indications/ products	Systemically- and locally-acting ectoparasiticidal and endectocidal VMPs (ATCvet codes QP53A, QP53B and QP54) authorised through the central and/or national procedures in the EU/EEA *Not within the scope are repellents, endoparasiticidal VMPs or pet care-related biocidal products for indoor use.*
Active substances	Ectoparasiticidal and endectocidal active substances contained in VMPs for the above-mentioned indications and products *Not within the scope are endoparasiticidal active substances contained in some of the above-mentioned products* A specific focus is put on substance (classes) for which (i) the most abundant use (currently and in the future) is anticipated; and (ii) for which scientific data indicate a higher risk to the environment (e.g. based on toxicity data, PBT properties and/or measured environmental concentrations)

Parameter	Scope
Routes of application	A specific focus is put on the routes of application mainly used for the above-mentioned products such as spot-on solutions, collars, shampoos, sprays, (chewable) tablets
Compartment	Outdoor environmental compartment *Not within the scope are the indoor environmental compartment and/or user/human safety*

3. Current situation in the EU/EEA: cat and dog population, authorised VMPs and active substances

The use of ectoparasiticidal VMPs is an integral part of an overall concept for the treatment and prevention of parasitic infestations to ensure animal welfare (e.g. nuisance from ticks and fleas) and animal health (e.g. cutaneous lesions, allergies or transmission of vector-borne diseases), but also to protect public health. Some of the most important zoonotic infectious diseases are associated with parasites transmitted from companion animals to man (Baneth *et al.*, 2016).

This chapter aims to provide an overview of the available knowledge on the cat and dog population as well as VMPs and active substances that fall within the scope of the present reflection paper. Pet population data are not only essential in order to be able to quantify the actual risks of zoonotic diseases attributable to companion animals and to develop sustainable interventions to prevent transmission to humans and livestock (CALLISTO, 2014), they also could be indicative for the environmental emission of active substances contained in ectoparasiticidal VMPs used in cats and dogs. As this chapter shall only give a general overview of the current situation in the EU/EEA, no specific focus is put on local peculiarities or current trends regarding popular breeds (e.g. animal size, length of fur), regional differences concerning the animal population (e.g. urban vs rural population), husbandry conditions (indoors vs free-roaming) or cross-border pet movement (e.g. travelling with pets and import of rescue animals), factors which could have an influence on the environmental exposure to ectoparasiticides.

3.1. Population of cats and dog in the EU/EEA

According to data published by the European Pet Food Industry association (FEDIAF, 2020), there are a total of 138 million cats and dogs in the EU/EEA, which equates to approximately one pet for every 3 inhabitants of the EU/EEA. In terms of population numbers, cats (75 million) are more numerous than dogs (63 million), although there are large differences between countries. For example, in Austria and France, the cat population is twice that of dogs, while in the Czech Republic and Spain, the dog population is twice as big as the cat population. In addition, pet ownership appears to be a growing trend in Europe, with the population having increased by 17% and 26% in the last ten years for cats and dogs, respectively. The increasing numbers are constant across the EU/EEA and the trend does not seem to have reached a plateau yet (FEDIAF, 2020). However, these data are not complete (data from some EU/EEA countries are missing) and do not include any information on ownership or the size of the stray animal population. The number of abandoned and homeless dogs and cats in all of Europe is estimated to be over 100 million animals, with some EU/EEA countries such as Romania or Italy having stray animal populations exceeding 1 million (Overgaauw *et al.*, 2020), albeit these figures cannot be fully substantiated. In addition, it appears that there is a significant problem with stray dogs in several EU Member States (Broom, 2017). Therefore, it is reasonable to assume that the management of ectoparasites conducted by community organisations, municipalities and non-governmental

organisations in such regions (e.g. in animal shelters and refuges) significantly differs from that of private pet owners.

3.2. Ectoparasiticidal VMPs used in cats and dogs

Ectoparasiticidal VMPs for companion animals can be used to treat and prevent infestations with ectoparasites such as fleas, mites, lice, ticks, or sand flies. In addition, most modern ectoparasiticides have a persistent efficacy and can thus be used prophylactically to prevent a re-infestation with these parasites (ESCCAP, 2022). Over the last decades, significant advances have been made in the development of new ectoparasiticidal VMPs for cats and dogs, which has resulted in a considerable increase in the number of available products to treat pets against ectoparasites (ESCCAP, 2022). However, in spite of these developments, a substantial amount of older molecules are still being used, presumably due to their lower cost (Beugnet and Franc, 2012) and because they continue to be effective. For example, it appears to be common practice for organophosphates, pyrethroids or amitraz to be periodically sprayed, mostly off-label, on dogs (and pen surfaces) in dog shelters to control ectoparasites (Brianti *et al.*, 2013). Nonetheless, the approach of antiparasitic treatment has evolved into preventing an infestation with ectoparasites and the transmission of diseases, mainly through the introduction of VMP spot-on formulations providing long-lasting activity (Beugnet and Franc, 2012). For instance, current products for the treatment of ectoparasites in companion animals provide efficacy against ticks and fleas for at least 1 month. Also, with the advent of active substances providing activity against both endo- and ectoparasiticides, the traditional differentiation between the two categories has become less clear and has led to the definition of the new substance class of "endectocides" (Selzer and Epe, 2021). At the same time, ease-of-use has been improved with the development of spot-on formulations (Beugnet and Franc, 2012). Vaccines against ectoparasites currently do not exist for companion animals in the EU/EEA and thus antiparasitic drugs will probably remain the only therapeutic and preventive solution for many years to come (Selzer and Epe, 2021) in addition to non-medicinal ectoparasiticidal control strategies, such as remediation and treatment of the pet's environment (disinfection, washing or treatment of contaminated blankets and resting places), avoidance of high burden areas, regular visual examination for ectoparasites and manual removal, if possible, or the isolation of contagious and affected animals (ESCCAP, 2022).

The following sections give an overview of the types of ecto- and endectocidal VMPs authorised for cats and dogs in the EU/EEA. In **Table 2** and **Table 3**, respectively, they are grouped according to their pharmaceutical form with information on the related ATCvet codes and the typical treatment intervals defined in the associated PI. ATCvet categories for which "major use" is anticipated are highlighted in bold. These have been categorised based on data received from a survey among national competent authorities (NCAs) of EU/EEA Member States conducted in Q1/2021 on authorised ectoparasiticidal VMPs for pets (for details on this survey see section 3.3). This shall convey a notion of which substances are predominantly included in specific types of VMPs.

Locally-acting ectoparasiticides

The majority of authorised VMPs in the EU/EEA containing locally-acting ectoparasiticidal substances are spot-on products, followed by collars, sprays and shampoos.

Spot-on products represent the biggest group of locally-acting ectoparasiticidal pet VMPs in terms of market authorisations. These products were introduced on the European market in the mid-1990s, and hundreds of spot-on products in different compositions and strengths corresponding to the size of the animal have been authorised in EU Member States since then.

To date, most of these products contain mainly the phenylpyrazole fipronil as active substance, either as single-substance VMP or in combination with the pyrethroid permethrin or the juvenile hormone mimetics methoprene or pyriproxyfen. In 2018, the phenylpyrazole pyriprole was introduced in addition to fipronil in a locally-acting spot-on product in the EU. In contrast, fewer locally-acting spot-on VMPs contain the neonicotinoids imidacloprid or dinotefuran (introduced in 2019) as active principle (either as single-substance or combination product). The remaining locally-acting spot-on products authorised in the EU/EEA contain either permethrin or, since 2019, the oxadiazine indoxacarb.

Collars in different formulations and sizes are the second largest product group among locally-acting ectoparasiticides authorised in the EU/EEA. The vast majority contain either organophosphates (mostly dimpylate) or pyrethroids (permethrin, deltamethrin, tetramethrin, flumethrin) as active substances. The latter are not only available as a single-substance products but also in combination with carbamates (e.g. propoxur) or neonicotinoids such as imidacloprid. In some Member States, collars containing amitraz, fipronil, tetrachlorvinphos or propoxur as single active substance are authorised. As collars release the active ingredient over an extended period of time, they need to be renewed less frequently than spot-on products and contain far greater amounts of active substance for comparable animal sizes, which is reflected in sales numbers of active substances (see section 4.1). The proportion of the active substance which is actually released onto the animal and which remains in the collar at disposal, is only known for individual products. However, for most collars, the exact quantities are not known. Based on the data from one study (Stanneck *et al.*, 2012) it can be assumed that more than half of the amount of active substance will remain in the collar at disposal (see section 4.2).

In addition, more traditional VMP formulations are still commonly authorised in a variety of product families, with cutaneous sprays predominately containing pyrethroids and fipronil, and shampoos predominately containing pyrethroids and propoxur as active substances.

Table 2. Locally-acting ectoparasiticidal VMPs for companion animals (nationally and centrally) authorised in the EU/EEA grouped by dosage form and ATCvet code.

Pharmaceutical form	ATCvet codes[1] ("major use"[2] in bold)	Typical treatment interval
Spot-on solution	**QP53AC-Pyrethrins and pyrethroids** **QP53AX-Other ectoparasiticides for topical use**	4 weeks
Collar	**QP53AC-Pyrethrins and pyrethroids** QP53AD-Amidines **QP53AE-Carbamates** **QP53AF-Organophosphorous compounds** QP53AX-Other ectoparasiticides for topical use	4–6 months
Cutaneous spray, solution	**QP53AC-Pyrethrins and pyrethroids** QP53AE-Carbamates QP53AF-Organophosphorous compounds **QP53AX-Other ectoparasiticides for topical use**	1–3 months
Shampoo	**QP53AC-Pyrethrins and pyrethroids** QP53AE-Carbamates	On demand
Other topical formulations (powder, emulsion, solution, etc.)	QP53AC-Pyrethrins and pyrethroids QP53AD-Amidines QP53AE-Carbamates QP53AF-Organophosphorous compounds QP53AX-Other ectoparasiticides for topical use	Variable

[1] Each VMP is allocated an ATCvet code. However, the classification is often not uniform, particularly for combination products, but also for substances such as fipronil and imidacloprid, for which no specific ATCvet code exist. VMPs containing these active substances are mostly assigned the code QP53AX ("Other") or—in the case of combination products—to pyrethrins and pyrethroids

[2] "Major use" based on the current authorisation status in the EU. Does not permit any conclusions on actual use or sales. "Major use" is anticipated if the active substance is contained in ectoparasiticidal VMPs for pets that are either (i) authorised centrally in the EU/EEA; and/or (ii) have at least 20 national authorisations in individual EU/EEA Member States.

Systemically-acting ectoparasiticides and endectocides

As detailed in **Table 3**, VMPs belonging to this group are classified as "ectoparasiticides for systemic use" (QP53B), as "endectocidal macrocyclic lactones" (QP54A), or as combinations with these. These products may be administered orally or topically (i.e. as spot-on application on the skin surface), typically on a monthly basis or less frequently. After the application, the active substances are steadily released into the animal's blood, thus maintaining levels of effective concentrations between the treatments.

Table 3. Systemically-acting ectoparasiticidal and endectocidal VMPs for companion animals (nationally and centrally) authorised in the EU/EEA.

Pharmaceutical form	ATCvet codes[1] ("major use"[2] categories in bold)	Typical treatment interval
Oral, parenteral and topical formulations	**QP53BC-Chitin synthesis inhibitors** **QP53BE-Isoxazolines** QP53BX-Other ectoparasiticides for systemic use **QP54A-Endectocide macrocyclic lactones**	1–3 months

[1] Each VMP is allocated a ATCvet code. However, the classification, is often not uniform, particularly for combination products. VMPs containing both ecto- and endectoparasiticidal active substances are assigned the ATCvet code QP54 ("Endectocides"). Systemically-acting ecto- and endectocides are available in oral, injectable and spot-on formulations.

[2] "Major use" based on the current authorisation status in the EU. Does not permit any conclusions on actual use or sales. "Major use" is anticipated, if the active substance is contained in ectoparasiticidal VMPs for pets that are either (i) authorised centrally in the EU/EEA; and/or (ii) have at least 20 national authorisations in individual EU/EEA Member States.

Ectoparasiticidal pet VMPs containing the chitin synthesis inhibitor lufenuron (QP53BC) entered the market in the mid-1990s and have since then been authorised in many EU/EEA Member States. This may indicate that they are still being used to a relevant extent in these countries.

However, currently, the isoxazolines (QP53BE) and related substances (for ease of reading termed isoxazolines hereafter), which were first introduced in the animal health market in 2014, are probably the most widely used class of substances within the group of systemically-acting ecto- and endectocidal VMPs. They are intended for oral or topical administration. Oral administration exhibits certain benefits over other application forms, such as the reduced potential for owner exposure to the included substances (relevant, for instance, for households with children) (Selzer and Epe, 2021). Currently, six isoxazolines (afoxolaner, esafoxolaner, fluralaner, sarolaner, lotilaner and tigolaner) are authorised in various VMPs for cats and dogs. These include single-substance products as well as combination products (e.g. with milbemycin, selamectin, eprinomectin, emodepsid or moxidectin as well as pyrantel or praziquantel) aimed at concurrently treating and preventing infestations with a variety of internal and external parasites. Nonetheless, topical formulations containing these substances also exist, which are easier to administer to certain pets (e.g. cats) when compared to oral products (Selzer and Epe, 2021). The indications for such combination products are usually restricted exclusively against mixed infections/infestations when several groups of parasite species (e.g. helminths, cestodes as well as ticks and fleas) are present at the same time (multiparasitism).

Endectocides for cats and dogs containing macrocylic lactones (predominantly avermectins and milbemycins) have been authorised in the EU/EEA since the early 1990s and 2010s, respectively. Though endectocidal active substances are effective against both internal and external parasites in principle, the substances ivermectin and milbemycin oxime are currently mostly approved for their endocidal effects in endectocidal pet VMPs. In recent years, a multitude of such combination products containing macrocyclic lactones indicated for the treatment and/or prevention of external as well as internal parasites (e.g. gastrointestinal and extraintestinal nematodes and cestodes) have been authorised throughout the EU/EEA. This reflects the trend towards the development and marketing of endectocidal VMPs effective against a large variety of parasites. From 2018 to 2021, eleven novel endectocidal VMPs (QP54A), either single-substance or combination products from seven different marketing authorisation holders (MAHs) were authorised via the centralised procedure in the EU/EEA. The outdoor use in baits containing active substances (e.g. deltamethrin, isoxazolines) as a measure to control fleas in wild animals, which provide a reservoir for fleas (and related diseases) in the environment, has so far only been reported outside the EU/EEA (Eads *et al.*, 2018; Rust, 2020).

Prudent use, treatment plans and owner compliance

The prudent use with regard to the appropriate indications, treatment intervals and the correct handling instructions are laid out in the PI of each VMP. In addition, information brochures and treatment recommendations from veterinary associations such as ESCCAP (2022) are publicly available. However, incorrect use and handling of the VMP as well as inappropriate treatment plans cannot be ruled out.

For example, an appropriate individual treatment and prevention plan for an animal should take into account a variety of different factors such as the lifestyle of the animal, travel plans, number of animals in the household, age, animal health, owner compliance and previous VMP use. Failure to follow these points could lead to incorrect use in terms of duration (too long or too short [seasonal] treatment) or an improper choice of product (e.g. unnecessary use of combination products for indications that are not relevant to the individual animal). In addition to the administration of the appropriate medication, other parasite control measures should also be taken into account, if possible. This includes, for instance, the disinfestation of the indoor environment, the avoidance of areas with a high parasite load (e.g. necessity to travel to areas with high parasite load) or the regular check of the animal for ectoparasites. Additionally, clinical aspects such as an appropriate diagnosis that confirms an infestation/infection or the assessment of the risk of infection should be considered.

Owner compliance with the correct handling instructions is not only important to ensure efficacy but may as well have an impact on environmental exposure pathways of the VMPs in question (see section 4.2 for details). For example, following the application of topically administered products, washing, bathing and grooming practices may further influence the stability and environmental distribution/leaching of the active substances applied. Also, the bioavailability, and hence the excretion of oral formulations can be influenced by feeding conditions at the time of administration (Zhou *et al.*, 2021). Ultimately, compliance with the RMMs specified in the PI for the protection of the environment, including the correct disposal (e.g. empty containers, used collars), is crucial.

Prescription status (OTC/POM) and distribution channels (retail/internet)

Prescription status and distribution channels are factors which may influence the choice, use, availability and sales of specific ectoparasiticidal VMPs for cats and dogs. In some Member States, ectoparasiticidal VMPs for pets are generally classified as prescription-only medicines (POM), whereas, in other Member States, many ectoparasticides may be purchased over the counter (OTC) without prescription based on national determinants. The prescription status of some VMPs might change with

the provisions outlined in Article 34 of Regulation (EU) 2019/6, which sets out the classification rules for VMPs, not excluding the environmental safety profile of a VMP. Guidance on the interpretation of Article 34 is provided by CVMP (EMA, 2022a).

The situation with regard to distribution channels of ectoparasiticidal VMPs is similarly diverse: While in some Member States such products may be purchased from veterinarians, pharmacies and authorised retailers only, fewer restrictions apply in other Member States. Furthermore, both the legal and illegal online sale of VMPs to the public are playing an increasingly important role in the supply of ectoparasiticidal VMPs. In some regions, cross-border sales within the EU/EEA and across EU borders may significantly influence the availability and supply with such VMPs.

Pharmacovigilance data and environmental incidents

In principle, it was already possible in the past to report potential environmental incidents following the use of veterinary medicinal products within the framework of the veterinary pharmacovigilance system (Article 73 of Directive 2001/82/EC). Reporting of potential environmental adverse events via the pharmacovigilance database was, however, not mandatory, and this information was therefore not collected centrally and is not easily accessible. From the available data, it can be assumed that suspected adverse events on the environment have only seldomly been reported for ectoparasiticidal VMPs for cats and dogs. With Regulation (EU) 2019/6, a Union pharmacovigilance system (maintained by Member States, the Commission, the European Medicines Agency [the Agency] and marketing authorisation holders) has been established, in which all suspected adverse events must be reported via the Union Pharmacovigilance Database, including any environmental incidents observed following the administration of a veterinary medicinal product to an animal. This is expected to improve data transparency regarding suspected adverse events in the future.

3.3. Active substances contained in ectoparasiticidal VMPs used in companion animals

To get an overview of which specific substances that are included in the currently authorised products in the EU/EEA, a survey was carried out in 2021 among Member States to retrieve information on authorised ectoparasiticidal VMPs for cats and dogs from national databases. Together with information on VMPs authorised via national, decentralised and centralised procedures, a dataset (product name, ATCvet code, MAH, active substance, target species, authorisation date, pharmaceutical form) of more than 1200 ectoparasiticidal VMPs was obtained and evaluated. This survey showed that, as of quarter 1 2021, about forty different ectoparasiticidal and endectocidal active substances were included in VMPs authorised for cats and dogs. **Table 4** gives an overview of these active substances along with a rough estimate of the extent of their use based on the valid authorisations of associated VMPs across EU/EEA Member States. Although the authorisation numbers do not permit any direct conclusions on the actual use or on sales volume, "major use" is anticipated for the purpose of this overview for those active substances included in ectoparasiticidal VMPs for cats and dogs that are either (i) authorised centrally throughout the EU/EEA; and/or (ii) have at least 20 national authorisations in individual EU/EEA Member States. In addition, **Table 4** contains information on the approval status of these active substances within the EU biocidal and pesticide/plant protection product (PPP) legal frameworks as well as key data on the chemical class. More detailed information is given in Annex I.

Table 4. Active substances with ectoparasiticidal and endectocidal activity included in VMPs for cats and dogs authorised in the EU/EEA (as of quarter 1 2021 for national, MRP and DCP and quarter 3 2022 for CP) as well their approval status in other legal frameworks (as of quarter 2 2022).

Active substance (synonym)	Chemical class[1]	"Major use" as VMP[2]	CAS no	Biocide approval status[3]	Biocide approval until[3]	PPP approval status[4]	PPP approval until / *(expired)*[5]
Locally-acting ectoparasiticides (ATCvet QP53A — Ectoparasiticides for topical use; synergists)							
Fipronil	Phenylpyrazole	**Yes**	120068-37-3	Approved	30.09.2023	*Not appr.*	*(since 30.09.2017)*
Pyriprole	Phenylpyrazole	**Yes**	1126-00-7	-	-	-	-
Imidacloprid	Neonicotinoid	**Yes**	138261-41-3	Renewal in progress	30.06.2023	*Not appr.*	*(since 01.12.2020)*
Dinotefuran	Neonicotinoid	**Yes**	165252-70-0	Renewal in progress	30.11.2024	*Not appr.*	-
Pyrethrum (pyrethrin)	Pyrethroid	No	8003-34-7	*No longer supported*	*(since 05.08.2020)*	Approved	31.08.2022
Bioallethrin	Pyrethroid	No	584-79-2	-	-	*Not appr.*	-
Phenothrin (sumitrin)	Pyrethroid	No	26002-80-2	Approved	31.08.2025	*Not appr.*	-
Tetramethrin	Pyrethroid	**Yes**	7696-12-0	*Initial evaluation in progress*	-	*Not appr.*	-
Permethrin	Pyrethroid	**Yes**	52645-53-1	Approved	30.04.2026	*Not appr.*	-
Deltamethrin	Pyrethroid	**Yes**	52918-63-5	Approved	30.09.2023	Approved	31.10.2022
Cypermethrin (transmix)	Pyrethroid	No	52315-07-8	Approved	31.05.2030	Approved	31.01.2029
Flumethrin	Pyrethroid	**Yes**	69770-45-2	-	-	-	-
Piperonyl butoxide	*(Synergist for pyrethroids)*	**Yes**	51-03-6	Approved	30.06.2028	*Not yet assessed at EU level*	-
Pyrodon (*N*-octyl bicyloheptene dicarboximide)	*(Synergist for pyrethroids)*	No	113-48-4	-	-	*Not yet assessed at EU level*	-
Methoprene	Juvenile hormone mimetic	**Yes**	153719-23-4	Approved	31.08.2025	*Not appr.*	-
Pyriproxyfen	Juvenile hormone mimetic	**Yes**	95737-68-1	Approved	31.01.2025	Approved	31.07.2035
Fenoxycarb	Juvenile hormone mimetic	No	72490-01-8	Approved	31.01.2023	*Not appr.*	*(since 31.05.2021)*

Active substance (synonym)	Chemical class[1]	"Major use" as VMP[2]	CAS no	Biocide approval status[3]	Biocide approval until[3]	PPP approval status[4]	PPP approval until / *(expired)*[5]
Indoxacarb	Oxadiazine	**Yes**	*173584-44-6*	Renewal in progress	30.06.2024	*Not appr.*	*(since 19.12.2021)*
Amitraz	Formamidine	No	33089-61-1	-	-	*Not appr.*	-
Crotamiton	Unclassified	No	483-63-6	-	-	-	-
Metrifonate (trichlorfon)	Phosphonate	No	52-68-6	-	-	*Not appr.*	-
Dimpylate (diazinon)	Organophosphate	**Yes**	333-41-5	-	-	*Not appr.*	-
Phoxime	Organophosphate	No	14816-18-3	-	-	*Not appr.*	-
Dichlorvos	Organophosphate	No	62-73-7	-	-	*Not appr.*	-
Tetrachlorvinphos	Organophosphate	No	22248-79-9	-	-	*Not appr.*	-
Propoxur	Carbamate	**Yes**	114-26-1	-	-	*Not appr.*	-
Carbaryl (carbaril)	Carbamate	No	63-25-2	-	-	*Not appr.*	-
Systemically-acting ectoparasiticides (ATCvet QP53B — Ectoparasiticides for systemic use)							
Lufenuron	Chitin synthesis inhibitor	**Yes**	103055-07-8	-	-	*Not appr.*	*(since 31.12.2019)*
Spinosad	Macrocyclic lactone (spinosyn type)	**Yes**	168316-95-8	Renewal in progress	31.10.2022	Approved	30.04.2023
Nitenpyram	Neonicotinoid	No	150824-47-8	-	-	*Not appr.*	-
Afoxolaner	Isoxazoline	**Yes**	1093861-60-9	-	-	-	-
Esafoxolaner[6]	Isoxazoline	**Yes**	1096103-99-9	-	-	-	-
Fluralaner	Isoxazoline	**Yes**	864731-61-3	-	-	-	-
Sarolaner	Isoxazoline	**Yes**	1398609-39-6	-	-	-	-
Lotilaner	Isoxazoline	**Yes**	1369852-71-0	-	-	-	-
Tigolaner[6]	Pyrazole	**Yes**	1621436-41-6	-	-	-	-
Systemically-acting endectocides (ATCvet QP54 — Endectocides)							
Milbemycin oxime	Macrocyclic lactone	**Yes**	93074-04-5	-	-	-	-
Ivermectin	Macrocyclic lactone	No	70288-86-7	-	-	-	-
Selamectin	Macrocyclic lactone	**Yes**	165108-07-6	-	-	-	-

Active substance (synonym)	Chemical class[1]	"Major use" as VMP[2]	CAS no	Biocide approval status[3]	Biocide approval until[3]	PPP approval status[4]	PPP approval until / *(expired)*[5]
Moxidectin	Macrocyclic lactone	**Yes**	113507-06-5	-	-	-	-
Doramectin	Macrocyclic lactone	No	117704-25-3	-	-	-	-
Eprinomectin	Macrocyclic lactone	**Yes**	123997-26-2	-	-	-	-

[1] Classification according to the BCPC Compendium of Pesticide Common Names (https://pesticidecompendium.bcpc.org/class_insecticides.html; accessed on 12 April 2022)
[2] "Major use" as VMP in cats or dogs, based on the current authorisation status in the EU. Does not permit any conclusions on actual use or sales. "Major use" is anticipated if the active substance is contained in ectoparasiticidal VMPs for cats and dogs that are either (i) authorised centrally in the EU/EEA; and/or (ii) have at least 20 national authorisations in individual EU/EEA Member States. Authorisation data retrieved from a CMDv Member States survey conducted in quarter 1 2021 as well as from the Veterinary MRIndex on the HMA website (https://mri.cts-mrp.eu/portal/home?domain=v) and from the EPAR table retrieved from the EMA website (https://www.ema.europa.eu/en/medicines/download-medicine-data); accessed on 19 February 2021 and 15 June 2022 respectively
[3] Retrieved from the ECHA biocidal active substances database (https://echa.europa.eu/en/information-on-chemicals/biocidal-active-substances/; accessed on 12 April 2022)
[4] Status under Regulation (EC) No 1107/2009
[5] Retrieved from the EU pesticides database (https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/active-substances/; accessed on 12 April 2022)
[6] No ATCvet classification in place as of 15 June 2022

In Annex I, these active substances are further classified based on their primary mechanisms of action (*primary targets*), and overlap with other uses ("multi-use substances") in the EU are briefly described, for instance biocidal use (e.g. for indoor/outdoor use or the use in agricultural practice) or PPP use. Where applicable, information on measures taken for specific active substances in other EU legislative frameworks and on relevant conclusions that have led to the implementation of such measures are provided.

For biocides and PPPs, it is shown that, due to environmental and health concerns, substance classes such as the neonicotinoids (e.g. imidacloprid, dinotefuran) and phenylpyrazoles (e.g. fipronil, pyripole) have largely replaced organophosphates (e.g. dimpylate, propoxur) and some traditional uses of pyrethroids (e.g. permethrin, deltamethrin) since the 1990s (R. Krieger, 2010). More recently, further active substances, including neonicotinoids, have started to be phased out as PPPs or are severely restricted as biocides, in particular due to their toxicity for pollinators (for details see Annex I). This trend is not observed to the same extent (if at all) for active substances used in VMPs for cats and dogs in Europe. While **Table 4** indeed shows that many of the old substances belonging to the carbamate, organophosphate or pyrethroid class have been replaced by newer ones, a considerable number of old molecules are still on the market, possibly because of their low cost.

The environmental effects and properties of most active substances used in ectoparasiticidal VMPs with the exception of the novel isoxazolines have been intensively studied in recent decades and are to a large extent well known. Relevant literature is readily available in the public domain. Therefore, more in-depth information on the persistence, bioaccumulation potential and ecotoxicological endpoints will be given only for selected active substances in chapter 5.

Available data on the environmental fate and exposure (emissions estimates and routes, monitoring data, exposure scenarios) of selected active substances included in ectoparasiticidal VMPs for cats and dogs will be discussed in chapter 4.

3.4. Conclusions on the current situation in the EU/EEA (population, VMPs, active substances)

Over the past decades, pet ownership has steadily increased across Europe and this trend is clearly continuing, although there are no robust data available on the overall pet population in the EU/EEA. Further information on the cat and dog population gathered at EU level which might influence the use-patterns and the exposure of the environment to ectoparasiticidal substances are scarce as well, including the number of owned and unowned animals (including stray and feral animals as well as those in shelters) or information on husbandry conditions (free-roaming or not; section 3.1).

Based on the data available on authorised ectoparasiticidal VMPs for dogs and cats, it can be assumed that, until recently, the market for such VMPs was dominated by locally-acting spot-on products followed by collars and sprays. It can also be assumed that, since the mid-2010s, systemic treatments have been increasingly sold and applied (section 3.2). These assumptions are supported by limited data available in the public domain (section 4.1).

There are clear trends towards the development and introduction of (i) formulations providing long-lasting activity; (ii) systemically-acting ectoparasiticidal VMPs that can be administered topically and orally; and (iii) combination products for the concurrent treatment and control of a variety of ecto- and endoparasites (multiparasitism). The substance class, which currently is most prominent in these developments, are that of the isoxazolines. At the same time, older molecules and formulations are still being used, presumably due to their low cost. For old products, there are large differences in the palette of approved VMPs within the EU/EEA, both in terms of pharmaceutical form and in terms of active substances included (section 3.3). Locally-acting spot-on products predominantly contain permethrin and fipronil and to a lesser extent imidacloprid as active substance, some in combination with methoprene or pyriproxyfen. In collars, which contain much higher absolute amounts of active ingredient than spot-on or oral formulations, the principal active substances authorised are pyrethroids, dimpylate, imidacloprid and the carbamate propoxur, either as single-substance or in combination with other substances. Cutaneous sprays predominately contain pyrethroids and fipronil as active substances, whereas shampoos most commonly contain pyrethroids and propoxur (section 3.2 and 3.3).

Establishing an individual treatment plan tailored to the needs of the individual animal is complex and might require veterinary advice. The extent of off-label use cannot be quantified, as the prescription status and distribution channels for VMPs with ecto- and endectoparasiticidal activity for companion animals vary greatly within the EU/EEA (section 3.2).

4. Environmental fate and exposure

4.1. Emissions estimates based on sales data and cat and dog populations

Emission estimates cannot be readily calculated because, unlike for antimicrobials under the ESVAC project (EMA, 2022b), there is no surveillance system in place on the veterinary sales of (ecto-)parasiticides in the EU/EEA. Sales data of ectoparasiticidal VMPs are usually not published in the public domain by marketing authorisation holders and consequently, no sales data are reported, collected and processed systematically along with animal population data. Although point (d) of Article 55(2) of Regulation (EU) 2019/6 requires data on the annual volume of sales of VMPs to be collected in the "Union Product Database" (UPD), such data are considered commercially confidential information and are therefore not visible to the general public in accordance with Article 11 of Commission Implementing Regulation (EU) 2021/16. In addition, as it is rarely reported in peer-reviewed literature, it is challenging to obtain country or state-specific information on annual trends of

quantities of ectoparasiticidal active substances used. Furthermore, in those countries/states in which information is indeed available, quantities are often measured in different ways (sale, usage, products shipped, etc.) and comparisons of absolute amounts are not straightforward, although trends can be identified (Simon-Delso *et al.*, 2015). Publicly available sales data and estimates available for imidacloprid and fipronil in UK (still member of EU during reporting period) and the Netherlands are summarised in **Table 5** and in the text thereafter as exemplary substances.

Table 5. Sales figures of imidacloprid and fipronil used in VMPs for companion animals reported in the public domain, together with cat and dog population numbers.

Country: description	Amount sold [kg/year]	Reporting period	Source	Reference	Population of cats/dogs [in millions]
Imidacloprid					
UK: total amount in VMPs	33,036	1997–2019(?)	VMD, FOI request	(Perkins, Whitehead, Civil, *et al.*, 2021)	-
UK: total amount in VMPs	3,910	2015	VMD, FOI request	(Anthe *et al.*, 2020)	7.4/8.5[1]
UK: total amount in spot-on and collars of 1 manufacturer only	4,000	2017	Estimate based on sales figures (Bayer)	(Anthe *et al.*, 2020)	8.0/8.5[2]
NL: neonicotinoids in flea and tick agents for cats and dogs	500–1,500	2018–2019	Estimate based on sales figures (FIDIN)	(Montforts *et al.*, 2021)	3.1/1.9[3]
Fipronil					
UK: total amount of fipronil sold in VMPs	27,471	1994–2019(?)	VMD, FOI request	(Perkins, Whitehead, Civil, *et al.*, 2021)	-
NL: sales of phenylpyrazoles in flea and tick agents for cats and dogs	500–1,500	2018–2019	Estimate based on sales figures (FIDIN)	(Montforts *et al.*, 2021)	3.1/1.9[3)]

[1] Retrieved from: https://www.pfma.org.uk/pet-population-2015 (accessed on 24 January 2022)
[2] Retrieved from:https://www.pfma.org.uk/pet-population-2017 (accessed on 24 January 2022)
[3] Retrieved from:https://dibevo.nl/kenniscentrum/huisdieren-in-nederland (accessed on 24 January 2022)

Sales data of flea and tick VMPs for dogs and cats in the Netherlands (2018–2019)

In the Netherlands, the Dutch Animal Health Industry Organisation (FIDIN) has provided sales figures for a review on veterinary pharmaceuticals in the environment. An outline of the sales data from this review on flea and tick agents for cats and dogs is presented in a report as part of the "Water Quality Knowledge Impulse" programme (Montforts *et al.*, 2021). **Figure 1** gives an overview of active substance sales broken down by target species (blue), substance class (red) and application route

(green), respectively. Although the data are incomplete and only represent a rough classification, they provide enough information to allow for a general assessment of the situation in the Netherlands. This only covers sales by veterinarians, pharmacies and wholesale. Products only sold at (pet) shops, garden centres and personal care product retailers are not included.

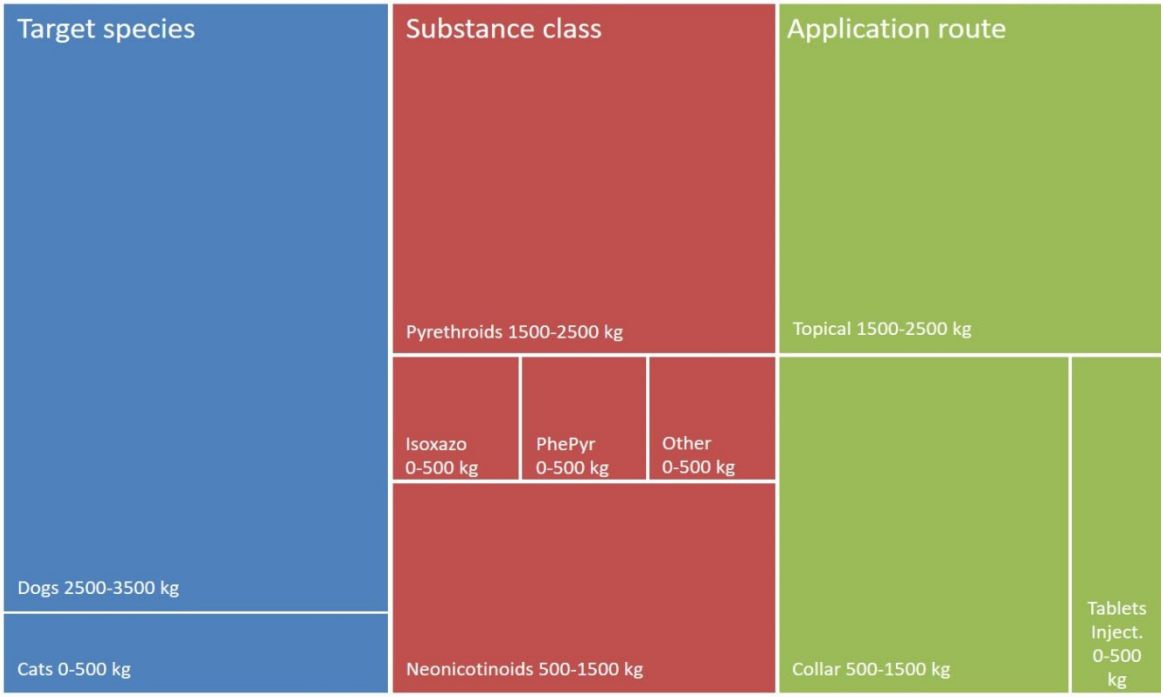

Figure 1. Dutch sales data of flea and tick agents in 2019, registered by FIDIN (as kg active ingredient per year). Sales data are shown in classes (0–500, 500–1500, 1500–2500 and 2500–3500 kg). The total is broken down by target species, substance class and application route. The registration by the FIDIN does not cover the total sales of the VMPs in the Netherlands. (Montforts et al., 2021)

It can be deducted from **Figure 1** that significantly more substance amounts are used in dogs than in cats (blue box), even though the cat population is more than 50% larger than the dog population in the Netherlands according to FEDIAF (2020) estimates. The active substance sales in the Netherlands is dominated by pyrethroids and neonicotinoids (primarily imidacloprid). Interestingly, the amounts of neonicotinoids sold are much higher than those of phenylpyrazoles (primarily fipronil), although both substances are used equally in spot-on products. This most likely reflects the high amounts of active ingredient used in collars. In 2018–2019, the quantitiy of substances used in cutaneous products was still a multiple of those used in oral products (green box). This ratio may have shifted in the meantime with the availability of additional options for systemic treatment, although some of these can also be applied cutaneously.

Sales data of imidacloprid in pet VMPs in the United Kingdom since 1997 as well as in 2015 and 2017

In the UK, sales data for VMPs are not routinely published by the authorities, but can be retrieved with a Freedom of Information (FOI) request to the Veterinary Medicines Directorate (VMD). Such data, for the full period since 1997 as presented in **Table 5**, were retrieved and published by Perkins *et al.* (2021) for fipronil and imidacloprid, which in the UK are only authorised in VMPs for pets.

Anthe *et al.* (2020) have published the total amount of imidacloprid used in VMPs in the UK for 2015, which amounted to 3910 kg. Independently of this, Anthe *et al.* (2020) analysed the sales volume data retrieved from the main manufacturer of imidacloprid-containing spot-on collars together with pet

population numbers. These calculations show that almost half of the dogs and one third of the cats in the UK were treated with spot-on products containing imidacloprid. Under the assumption that one collar is used per year and pet in accordance with the marketing authorisation, sales figures for 2017 reflect the number of dogs and cats treated per year with a collar. Seasonality of use of the spot-on products is considered as well. Taking into account the different imidacloprid content in the products, the authors estimate that, in 2017, the total amount of imidacloprid used in VMPs sold by the main manufacturer alone in the UK was about 4000 kg.

Estimation of annual emissions based on population numbers and assumed use

In order to get an indication of the actual tonnages of ectoparasiticidal substances used in pet VMPs throughout the EU/EEA, the following arbitrary estimation is made for selected active substances based on pet population numbers estimated by FEDIAF (2020), estimates on use (assumptions on percentage of population treated) and typical treatment protocols (see section 3.2.), following a "total residues approach" as outlined in VICH GL6 (i.e. all of the dose applied would be emitted unchanged into the environment). The fraction that actually ends up in the environment is not known. To account for regional differences (in other Member States less money may be spent on pet care), a significantly lower overall average use of 5% of the pet population numbers estimated by FEDIAF (2020) was arbitrarily assumed as EU/EEA average when compared to the data from the UK and the Netherlands referenced above for each of these product types (spot-ons, collars and systemics) and for one exemplary active substance (group) as follows:

- Under the assumption that 5% of the estimated EU/EEA dog population of 3.2 million animals are treated with a collar containing imidacloprid (average size with 3000 mg active substance) once a year, this could, in the worst case, result in emissions of roughly 9.5 tons imidacloprid per year from collars.
- Under the assumption that 5% of the estimated EU/EEA cat and dog population of 6.9 million animals would receive a spot-on formulation containing an average dose of 200 mg imidacloprid every four weeks in the summer season (6x), this could, in the worst case, result in emissions of roughly 8.3 tons of imidacloprid from spot-on products.
- Under the assumption that 5% of the estimated EU/EEA cat and dog population of 6.9 million animals are treated with a spot-on formulation containing an average dose of 200 mg fipronil every four weeks in the summer season (6x), this could, in the worst case, result in emissions of roughly 9 tons of fipronil from spot-on products.
- Under the assumption that 5% of the estimated EU/EEA cat and dog population of 6.9 million animals would receive a systemic isoxazoline formulation containing an average dose of 45 mg or 450 mg per treatment pipette every four weeks in the summer season (6x), this could, in the worst case, result in emissions of roughly 2 or 19 tons from isoxazoline-containing systemic products, respectively.

Based on data available to CAs, the magnitude of possible total emissions to the environment obtained for the exemplary substances fipronil and imidacloprid using the above worst-case assumptions gives an indication for the overall EU/EEA situation. Such estimations for other commonly used active substances such as some pyrethroids, organophosphates or carbamates are expected to be similar. With more detailed and robust information on pet populations and VMP use, such data could be calculated with greater accuracy for specific countries or regions and their pet populations.

4.2. Environmental exposure scenarios

Figure 2 shows possible pathways of exposure of the three identified final environmental compartments that receive ectoparasiticides from dogs: surface water, groundwater and soil. The emission routes have been mapped by consultants and professionals working with dogs and/or veterinary medicines (Mul *et al.*, 2021).

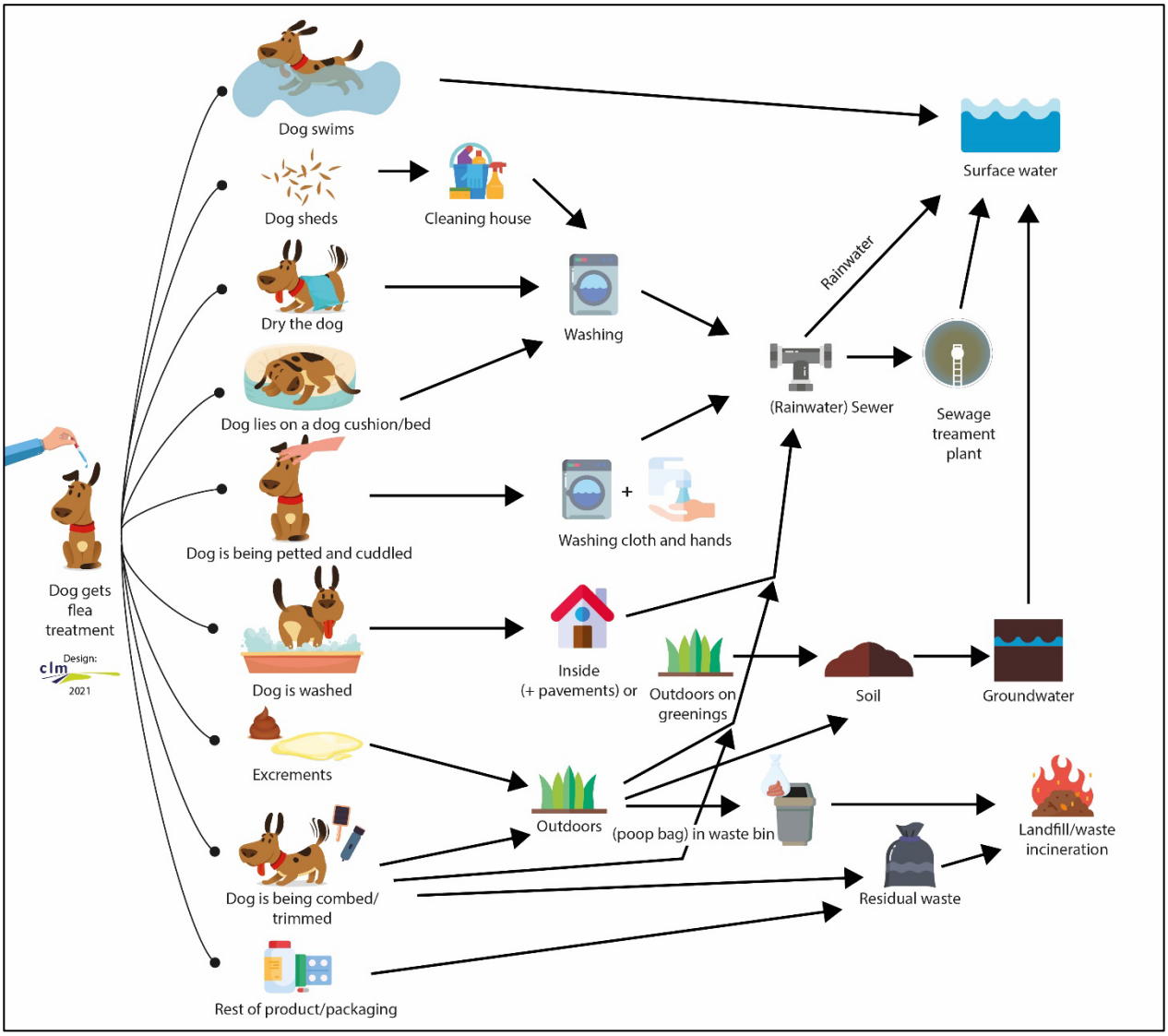

Figure 2. Emission pathways of flea and tick medication from dogs into the environment (with kind permission from CLM[1]) (Mul *et al.*, 2021)

The surface water compartment is where most pathways converge, so it is likely to have the highest exposure. In contrast to exposure scenarios that typically apply for VMPs used in farm animals, the excretion of active substance in faeces and urine by treated pets may not be the most important pathway, as most locally-acting active substances are poorly absorbed and faeces may be collected and disposed by the owners. Husbandry-related and behavioural exposure pathways appear to be more relevant in terms of quantity, with the surface water compartment being more frequently

[1] © CLM, publication number 1078, June 2021: Reduction of emissions to surface water of anti-flea products for dogs. Authors: Monique Mul, Margot Veenenbos and Jenneke van Vliet (all CLM) in cooperation with Melvin Faber (RIVM), Nanette van Duijnhoven (Deltares) and Mark Montforts (RIVM). https://kennisimpulswaterkwaliteit.nl/nl/publicaties/emissiereductie-naar-het-oppervlaktewater-van-antivlooienmiddelen-voor-honden

exposed than the others, mostly via indirect exposure after the release from a sewage treatment plant, although direct exposure should also be taken into account in case of animals swimming in surface waters.

The pathways of exposure to the terrestrial compartment with ectoparasiticidal pet VMPs are not well understood, and thus not elaborated on in **Figure 2**. One pathway suspected by Guldemond *et al.* (2019) is the exposure of birds to contaminated dog hair used for nesting. The potential transfer of veterinary flea products from dogs to the environment was explored by Diepens *et al.* (2023). Interestingly, contamination with ectoparasiticides was frequently demonstrated in samples from dogs untreated with these particular substances, suggesting widespread secondary transfer. Another pathway that has been reported in conjunction with parasiticidal VMPs, and which may have an impact on bees and pollinators, is via dust/air from excreta or sludge (Mahefarisoa *et al.*, 2021). For both pathways, neither the importance nor the impact that the residues of antiparasitics from pets may have on wildlife are known. A recent study, however, indicates, that the amounts of urine and faeces deposits in peri-urban ecosystems, such as forests, (semi-)natural grasslands, wet-lands and heath lands in populated areas, may be considerable, and the authors estimate that the resulting nutrient fertilisation by dog excreta may already influence biodiversity and ecosystem functioning considerably in these areas (De Frenne *et al.*, 2022). The effects of antiparasitic substances possibly present in the excreta in dogs or cats on terrestrial ecosystems have not been studied.

Emission scenarios for locally-acting and topically applied active substances

As described above, the environmental exposure pathways for products containing locally active substances can be very diverse and strongly dependent on environmental and other external conditions. Swimming in surface waters is the only direct exposure pathway of topical ectoparasiticidal VMPs into the environment. All the others are indirect exposure pathways and can only be quantified with difficulty. Only few studies have attempted to quantitatively investigate these for selected active substances and the available data is not yet sufficient to be able to reach robust conclusions. For example, Anthe et al. (2020) performed in-house studies with spot-on products and collars containing imidacloprid. Petting tests and further investigations were carried out, including collar immersion tests and tests with washed and vacuumed cat bedding. Teerlink *et al.* (2017) analysed the fiprole (i.e. fipronil and fipronil degradation products) content in the rinsate of dogs washed either 2, 7, or 28 days after application of a fipronil-containing spot-on product. The total mass of fiproles measured in the rinsate ranged from 0.2–86.0% of the mass applied. The average percentage of fiproles detected in the rinsate generally decreased with increasing time from the initial application. Yet other studies have investigated the influence of grooming behaviour and environmental aspects (sun exposure, bathing and shampooing, swimming) on the surface distribution of spot-on products containing pyrethroids in the *stratum corneum* and on hair (Pfister and Armstrong, 2016; Bäumer and Baynes, 2021). Other studies have been conducted to quantify the transferable amounts of amitraz, indoxacarb, fipronil, permethrin and methoprene from the animal's coat to humans and the indoor environment (Nichols *et al.*, 2014; Litchfield *et al.*, 2015; Case *et al.*, 2016).

Mul *et al.* (2021) discuss the issue of treated pets being a source of ectoparasiticides in the environment as well as their owners. The authors note that the transfer of the active substance from the treated animal to house dust, household textiles and clothing as well as to hands (via petting) can explain that the substances are found in the owner's/residents' urine, in house dust, hair and in textiles (Bigelow Dyk *et al.*, 2012; Gooijer *et al.*, 2019; Testa *et al.*, 2019; Mantingh, 2021; Oerlemans *et al.*, 2021; Rodzaj *et al.*, 2021). They consider it plausible that this exposure of hands, house dust and textiles subsequently leads to exposure of the grey wastewater through washing and, after ingestion, through urine and faeces. The same applies to the application of shampoos, where the substances can end up in the surface water via sewage water, but there are no data to model the

house dust load to the wastewater. There is too little knowledge about the origin of house dust to make a mass balance, or to map, for example, the load of the same substances (for example when used as plant protection products) that reach the house dust from the environment (Vermeulen et al, 2019). Mul *et al.* (2021) conclude that it is possible that part of the administered dose is lost via skin contact (petting, textiles) and house dust and then may subsequently reach the wastewater via the hand washing and laundry effluents. However, there is insufficient data to calculate a loss fraction or a load. This route can only be assessed qualitatively.

Stannek et al. (2012) studied the release of active ingredients from collars applied for ectoparasite control in dogs and cats and the remaining content in the collar over time under laboratory and field conditions. The results show a slow and steady release of imidacloprid and flumethrin over 8 months, at which time the collars still contained approximately 60 and 80% of the imidacloprid and flumethrin starting concentration.

Emission scenarios for systemically-acting active substances

For systemically-acting active substances, no dedicated studies have been conducted so far to quantitatively assess environmental emissions, although publicly available data from pharmacokinetic (PK) studies conducted for the marketing authorisation of the respective products provide starting points for a quantitative risk assessment.

As an example, for the novel isoxazolines, the excretion of unchanged parent via faeces over a period of several weeks after administration may be regarded as the main exposure route into the environment (see **Table 9** in Annex I). Therefore, environmental exposure will very much depend on pet waste management, i.e. depending on whether excrements end up in landfill/waste incineration, the sewage system or outdoors, as would be the case for all free-roaming pets and a fraction of the companion animals as well. Furthermore, available bioavailability data from PK studies performed with isoxazolines give reason to assume that the environmental exposure may also be influenced by other factors such as feeding status (fed/fasted) and route of administration (oral/topical). This may particularly be the case in the initial phase after administration, as the bioavailability of oral isoxazolines ranges from 8.4% to 100% depending on the feeding condition, whereas the bioavailability of topical isoxazolines is about 25% (Zhou et al., 2021).

Therefore, a greater proportion of the active ingredient may be excreted in faeces in the initial phase after administration than in subsequent weeks. For topical formulations, additional exposure routes similar to those of spot-on products may need to be considered immediately after application. Data supporting these assumptions are scarce, although data from a very recent swimming experiment in an artificial pool showed that the transfer of fluralaner from dogs to the aquatic environment may lead to water concentrations above the surface water limit of 0.47 ng/L (Diepens *et al.*, 2023).

4.3. Environmental monitoring data: case studies

Monitoring data has been collected through various programmes, most notably surveillance programmes following the coming into force of Directive 2013/39/EU[2] amending the WFD[3], which listed imidacloprid among the surface water watch list (WL) substances between 2016–2020. Further measurement programmes were also carried out under other programmes at national (UK, Netherlands, Spain, France, Germany) and transnational levels such as for the Danube (Liška *et al.*, 2021) or the Rhine river basin (RIWA-Rijn, 2021).

For imidacloprid, fipronil, and dimpylate (diazinon), available monitoring data are discussed in the following sections. These active substances were selected not only because monitoring data are available, but also because a reliable estimation regarding their contribution to environmental concentrations when contained in VMPs for cats and dogs is more likely to be achieved since their non-VMP uses are limited, unlike, for example, in the case of many pyrethroids. Below a rough overview on the relevant key data is given, with more details provided in Annex I.

Background imidacloprid:

- The use and sales of imidacloprid as PPP was prohibited for most agricultural applications in 2018 and is currently being or has already been phased out in the EU/EEA countries (Annex I).
- Biocidal products containing imidacloprid are intended for professional use in bait formulations only (e.g. by pest control operators, farmers).
- Imidacloprid is currently the only active substance contained in ectoparasiticidal VMPs for cats and dogs on the EU surface water WL (2016–2020).
- Wide use in ectoparasiticidal collars and spot-on products for cats and dogs.

Background fipronil

- The use and sale of fipronil were prohibited for most agricultural applications in 2014 successively restricted in the following years (due to transition periods) in each Member State (Annex I).
- The biocidal use of fipronil is strongly restricted and intended for professional indoor use only.
- Fipronil was proposed as candidate for the next surface water WL due to P(ersitent), v(ery)Persistent and T(oxic) properties (JRC, 2020).
- Wide use in ectoparasiticidal spot-on products for cats and dogs.

Background dimpylate (diazinon)

- Diazinon has been banned in the EU for the use as PPP since 2007 and for the use as biocide since 2010.
- No longer in use in ectoparasiticidal VMPs for food-producing animals (mostly sheep dips) in many, but not all EU/EEA Member States.
- Still authorised in ectoparasiticidal collars for cats and dogs in some EU/EEA regions.

[2] Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy. OJ L 226, 24.8.2013, p. 1–17.
[3] Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy. OJ L 327, 22.12.2000, p. 1–73.

Case study 1: Presence of imidacloprid, fipronil and dimpylate in the Danube river basin: findings of the fourth Joint Danube Survey (4JDS)

Imidacloprid is a substance with broad application in horticulture and agriculture and in widespread use in the Danube River Basin. It was detected in 50 out of 51 samples, surpassing the proposed PNEC value of 0.0083 µg/L in 7 samples (in Devín [SK], Budapest and Tass [HU], Tisza mouth [RS], Jantra mouth and Russenski Lom mouth [BG] and Giurgiulesti [MD/RO]). These elevated concentrations were mostly found in tributaries with a maximum of 0.040 µg/L in Russenski Lom. In general, imidacloprid concentrations in the Danube increase from the upper to the lower basin (Liška *et al.*, 2021).

From the data reported, it can be concluded that agriculture is the main source of imidacloprid in surface waters. The downstream increase of concentrations is most likely due to emissions from the vast agricultural landscape which starts on the borders between Austria (AT), Slovakia (SK) and Hungary (HU), extends through Hungary and Vojvodina (northern Serbia) and then along the flatlands between Bulgaria (BG) and Romania (RO). Based on the broad use in agriculture, it seems unlikely that imidacloprid sourced from VMP applications would significantly contribute to the measured surface water concentrations.

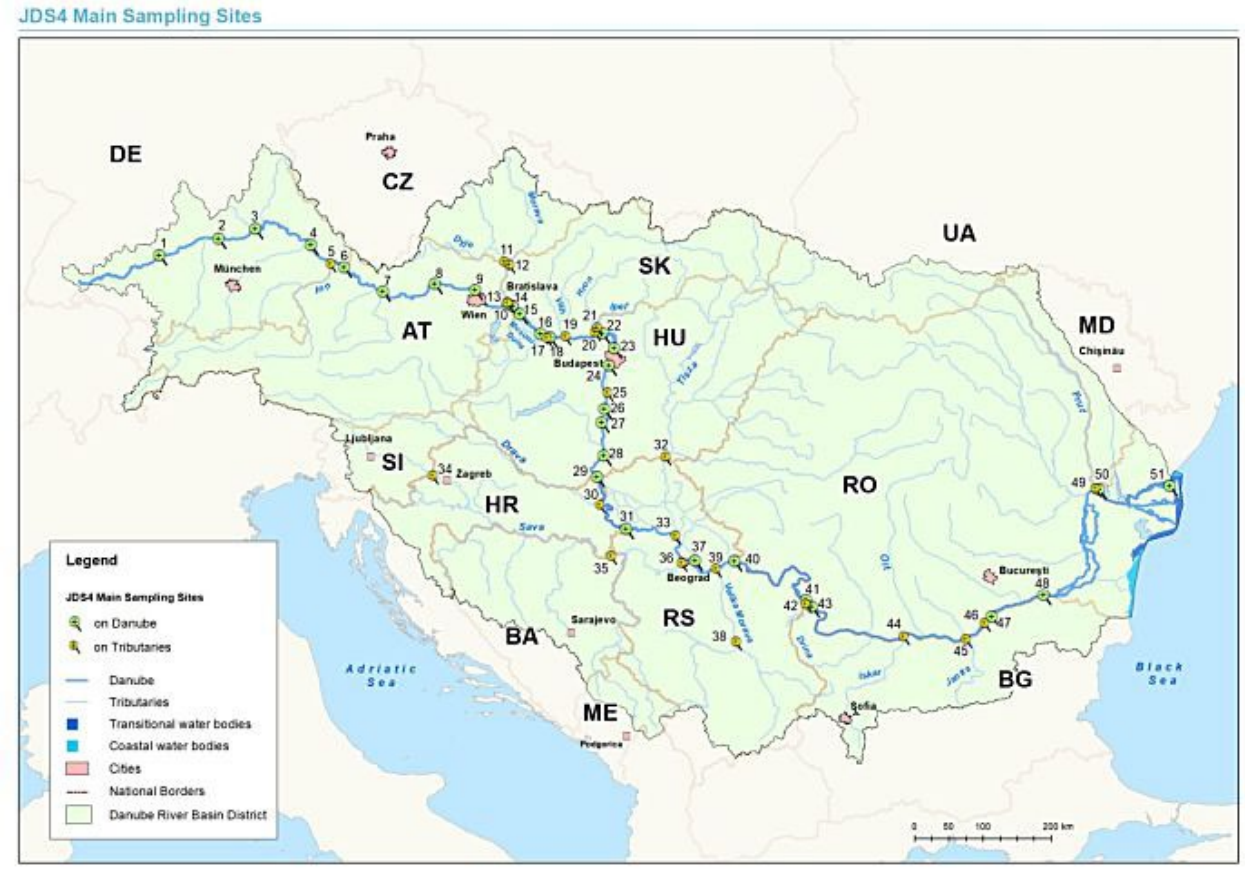

Figure 3. Fipronil as one of 19 river basin-specific pollutants (RBSP) was found in wastewater treatment plant effluents, but not in any of the surface water samples. Among 33 analyses, 14 indicated a fipronil concentration above the limit of quantification (with kind permission from ICPDR[4]) (Liška *et al.*, 2021).

The use of fipronil as PPP in the EU is prohibited, although that is not necessarily the case for Serbia (RS) and Moldova (MD). The absence of fipronil in surface water and its presence in wastewater

[4] © International Commission for the Protection of the Danube River (ICPDR); available at http://www.danubesurvey.org/jds4/jds4-files/nodes/ck/images/JDS4_Main_Sites_Overview.jpg

treatment plant (WWTP) effluents might indicate that the source of emission is the use as biocide and as VMP. The estimation of share between these two types of use would not be possible without information on the tonnage use in each of these markets (Liška *et al.*, 2021).

Dimpylate (diazinon) is listed as Danube river basin-specific pollutant (RBSP) and was detected in 12 of the 51 sampling sites, with the lowest PNEC value of 0.001 µg/L being exceeded at 9 sites (mainly in tributaries of the middle and lower Danube section with a maximum concentration of 0.0028 µg/L in the Tisza River (RS). Although ectoparasiticidal collars are stated as the only legal source for diazinon in that region (Liška *et al.*, 2021), other sources of supply should be considered as well to explain these concentration levels.

Case study 2: Imidacloprid in Spanish WWTPs

Environmental contamination with imidacloprid might occur via a number of sources (e.g. PPPs, biocides and VMPs) and strict regulations have been established in the EU during the last two decades to control the environmental concentration levels of imidacloprid (among other water contaminants) in the water compartment. In Spain, monitoring of imidacloprid by following the indications reflected in the WFD have been performed by the Ministry of Environment (MITECO) since 2018 and have been extended until (at least) 2021. During this timeframe, water samples were taken from the effluents of 16 sewage water treatment plants (SWTPs) and 20 water courses downstream of these SWTPs in 10 different river basin districts. EFSA regulatory acceptable concentrations (RACs; (EFSA, 2014)) were used as a reference and compared with the imidacloprid residues detected for risk characterisation (RQ). In case the ratio between the residues detected and the RAC was above 1, a risk for the environment was concluded.

Quantifiable levels of imidacloprid were detected in almost all SWTPs and water courses sampled in Spain in 2018 and 2019. An acute risk in the effluents was identified in 6 out of 16 SWTPs in 2018 and in 1 out of 16 SWTPs in 2019, respectively. No acute risk was identified in the waterways sampled in 2018 and 2019. Regarding the chronic risk, values above 1 were identified in 12 out of 16 SWTPs and in 8 out of 20 water courses in 2018 as well as in 15 out of 16 SWTPs and in 12 out of 20 waterways in 2019. Of particular note is the chronic risk identified in almost all effluents of SWTPs sampled (de la Casa-Resino *et al.*, 2022).

In order to allow the management of the identified risks for the environment, reflections about the potential sources of imidacloprid residues were performed. The conclusions indicate that PPPs and VMPs could be the main sources of imidacloprid in the aquatic environment, while the contribution of biocides is almost negligible due to the formulation of such products. However, as the use of imidacloprid in PPPs is no longer authorised, special attention should be paid to the residues having been detected in the following years (i.e. 2020 and 2021) to obtain a more reliable conclusion on whether VMPs are a significant source of emission.

Case study 3: Fipronil and imidacloprid in English WWTPs and rivers

Using data from the Environment Agency, Perkins et al. (2021) examined the occurrence of fipronil, fipronil metabolites and imidacloprid in 20 English rivers from 2016–2018 as indicators of the potential contamination of waterways from their use as ectoparasiticides in pets. Water samples were collected by the Environment Agency as part of their chemical surveillance programme and analysed. A total of 3861 samples were examined, and the significance and potential sources of contamination were assessed. Fipronil, fipronil sulfone, fipronil sulfide (collectively known as fiproles) and imidacloprid were detected in 98.6%, 96.5%, 68.7% and 65.9% of samples, respectively. Across the river sites sampled, the mean concentrations of fipronil (17 ng/L, range < 0.3–980 ng/L) and fipronil sulfone (6.5 ng/L,

range < 0.2–39 ng/L) were 5.3 and 38.1 times higher than the environmental quality standards based on chronic toxicity of 3.2 and 0.17 ng/L, respectively. Imidacloprid had a mean concentration of 31.7 ng/L (range < 1–360 ng/L), which was below the chronic toxicity environmental quality standard of 35 ng/L, although seven out of 20 sites exceeded that limit. Chronic risk quotients indicate a high environmental risk to aquatic ecosystems emanating from fiproles and a moderate risk emanating from imidacloprid. Sites immediately downstream of WWTPs showed the highest levels of fipronil and imidacloprid, supporting the hypothesis that potentially significant quantities of pesticides from veterinary flea products may be entering waterways via household drains (Perkins, Whitehead, Civil, *et al.*, 2021).

Anthe *et al.* (2020) analysed the same monitoring data collected under the WFD between 2016 and 2018, with the aim to investigate the potential contribution of VMPs by developing a model for predicting emissions from WWTPs from the use of spot-on and collar products for cats and dogs. Due to the absence of appropriate exposure models for VMPs, the model was built based on the principles used within the environmental exposure assessment of biocidal products. Three emission paths were considered to be the most likely routes for repeated emissions to waterways from the use of spot-on and collar VMPs, i.e. transfer to pet bedding followed by washing, washing/bathing of dogs and walking of dogs in the rain. The developed model was used to calculate imidacloprid concentrations in surface water after discharge from WWTPs. Realistic worst-case input parameters were deduced from sales and survey data (see section 4.1.) and experimental studies. Modelled total concentrations in surface water for each pathway ranged from 0.84–4.8 ng/L. The calculated concentrations did not exceed the ecotoxicological thresholds for the most sensitive aquatic invertebrate organisms and were found to be much lower than the monitoring data for river water. For example, the calculated concentration from the bathing/washing of dogs was less than 3% of the highest levels of imidacloprid measured in surface waters. The authors concluded that the modelled data indicate that VMPs containing these substances make only a very small contribution to the levels of imidacloprid observed in the frame of the UK water monitoring programme. Furthermore, calculated concentrations did not exceed ecotoxicological threshold values, indicating acceptable chronic safety to aquatic organisms.

These conclusions were challenged by Perkins et al. (2021). They claim shortcomings in the methodology—including the implicit assumption that imidacloprid applied to pets is available for release to the environment for 24 h only and failure to incorporate site-specific sewage effluent data relating to measured levels—and raise questions about the conclusions drawn. Adjusting for these and other deficiencies, the authors find that the model appears consistent with the conclusion that emissions from VMPs may greatly exceed ecotoxicological thresholds and contribute substantially to imidacloprid waterway pollution in the UK.

Case study 4: Imidacloprid and fipronil in Dutch WWTPs and surface water

In the Netherlands, monitoring data from several different databases and programmes (Rhine river, rural surface waters, WWTP effluents and other screening programmes) are available. Imidacloprid and fipronil were detected at multiple monitoring sites, including locations for drinking water production, rural sites and WWTPs (**Tables 6** and **7**). These observations indicate that the long-term environmental quality standard AA-EQS (8.3 ng/L for imidacloprid and 0.07 ng/L for fipronil) are exceeded at multiple sites, indicating a risk. However, data from none of these monitoring sites allows for making a distinction between the different uses of imidacloprid and fipronil. For example, in 2017, inspections in the Netherlands revealed a widespread misuse of fipronil as a biocide in poultry farming, where it was used to treat and prevent red mite infestations (Sok *et al.*, 2020). This misuse could partly explain the observed environmental concentrations. Nevertheless, as both substances are also observed in WWTPs with (mainly) domestic input, the contribution from their use as active ingredients in VMPs for the treatment of companion animals cannot be excluded. The removal efficiencies for

807 imidacloprid and fipronil from WWTP influent were determined to be 37% and 31% only, in contrast to
808 permethrin, for which a removal efficiency of 98% was estimated (Mul *et al.*, 2021).

809 **Table 6.** Overview of imidacloprid monitoring data in the Netherlands

Occasion	Observation	Year	Reference
Monitoring locations in the Rhine river delta	Average range: 1.46–3.34 ng/L Total range: < LOD–5.37 ng/L	2020	(RIWA-Rijn, 2021)
Rural location for monitoring of plant protection products	Exceedance of the AA-EQS of 8.3 ng/L at 84 out of 500 locations	2019	www.bestrijdingsmiddelenatlas.nl (accessed on 24 January 2022)
Monitoring in the Scheldt delta	Exceedance of the AA-EQS at two WWTPs, of which one is domestic	2009–2013	(Visser and Van Der Wal, 2014)
Monitoring in six WWTPs over two occasions	Concentrations in the more rural WWTPs: 0.027–0.065 µg/L Concentrations in WWTPs with high industrial input: 0.084–0.18 µg/L Concentrations in mid-sized towns with intermediate industrial input: 0.043–0.067 µg/L	2017	(Baltussen, 2018)
Broad screening of the Meuse river	19% of the surface water samples (n = 439) above the AA-EQS 90% of the influents and effluents of WWTPs above the AA-EQS Also found in groundwater	2010–2016	(Lahr *et al.*, 2019)

810 **Table 7.** Overview of fipronil monitoring data in the Netherlands

Occasion	Observation	Year	Reference
Rural location for monitoring of PPPs	Exceedance of the AA-EQS of 0.07 ng/L at 35 out of 380 locations	2019	www.bestrijdingsmiddelenatlas.nl
Monitoring in the Scheldt delta	Exceedance of the AA-EQS at two WWTPs, one of which was related to cockroach control	2009–2013	(Visser and Van Der Wal, 2014)
Monitoring in six WWTPs over two occasions	Not detected (LoQ of 1 µg/L)	2017	(Baltussen, 2018)
Broad screening of the Meuse river	1.7% of all surface water samples above the AA-EQS 43% of all samples in effluent from WWTPs above the AA-EQS	2010-2016	(Lahr *et al.*, 2019)

Case study 5: French watch list monitoring campaigns: imidacloprid

In France, the monitoring of the WL substances pursuant to the WFD was implemented at 26 sampling stations of the national surveillance network. Four monitoring campaigns between the beginning of 2016 and the end of 2017 were performed. In order to take into account this seasonal variability, two sampling periods were chosen. Thus, a total of four sampling campaigns were organised, 2 sampling campaigns in contrasting conditions (spring and late summer/fall) per year (2016 and 2017). In each basin, the sites were classified according to the level of potential presence of the substances on the list and selected to be representative of the main types of sources: agricultural (8 stations), urban (10 stations) and industrial (8 stations) (Togola *et al.*, 2019).

Table 8. Overview of imidacloprid monitoring data in France:

Substance	Number of quantified values	Average concentration [ng/L]	Median concentration [ng/L]	Maximum concentration [ng/L]	Minimum concentration [ng/L]
Imidacloprid	32/104	29,7	16,0	214	10

Imidacloprid, included in the WL for its use as PPP, was detected at 32 of 104 sites as shown in **Table 8**. Detailed information on the nature of these sites, which would allow interpretation of the data with regard to potential sources of the imidacloprid concentrations is not available, although this could change with future data acquisitions, following the ban of the use of imidacloprid as PPP in France in September 2018. The future data acquisitions will perhaps allow to see whether the changes in practice are already visible (i.e. a decrease in imidacloprid concentrations is expected as a result of the above-mentioned ban; Togola *et al.*, 2019).

Case study 6: German small water monitoring pilot study

The pilot study "Kleingewässermonitoring" (small water monitoring) was successfully implemented as a two-year monitoring programme of residues of plant protection products (PPPs) in small streams. The chemical pollution and biological status of small streams in the agricultural landscape was investigated in-depth between April and July in 2018 and 2019 in more than 100 stream sections in 13 federal states in Germany. In addition to the collection of grab water samples according to the WFD, event-based water samples were taken, which represent short-term pulse concentrations of pesticide residues following precipitation events. Other anthropogenic stressors such as poor structural quality of watercourses, excess nutrients and oxygen depletion were also recorded for the whole data set. The biological investigations included sampling of the aquatic invertebrate community and the algal community as well as ecosystem functions in the small streams (Liess *et al.*, 2022).

The most frequent RAC exceedances occurred with the active ingredient fipronil (6% of all grab samples) and the substances of the neonicotinoid group, in particular imidacloprid (3%) and clothianidin (1%). For fipronil, flea control agents for companion animals are stated as one of several potential sources by the authors (Liess *et al.*, 2022).

Case study 7: Imidacloprid and fipronil in the San Francisco Bay area (CA, USA)

Urban pest control insecticides—specifically fipronil and its 4 major degradation products (fipronil sulfone, sulfide, desulfinyl and amide) as well as imidacloprid—were monitored during drought conditions in 8 San Francisco Bay (San Francisco, CA, USA) WWTPs. In influent and effluent, fipronil, fipronil sulfone, fipronil sulfide and imidacloprid were ubiquitously detected in concentration ranges of 13–88, 1–28, 1–5 and 58–306 ng/L, respectively. Partitioning was also investigated: in influent, 100%

of imidacloprid and 62 ± 9% of total fiproles (fipronil and degradation products) were freely present, while the balance was bound to filter-removable particulates. The insecticides persisted during wastewater treatment, regardless of the treatment technology utilised (imidacloprid: 93 ± 17% remaining; total fiproles: 65 ± 11% remaining), and partitioned also into sludge (3.7–151.1 µg/kg dry weight as fipronil) accounting for minor losses of total fiproles entering WWTPs. The load of total fiproles was fairly consistent across the facilities but fiprole species varied. This first regional study on fiprole and imidacloprid occurrences in raw and treated sewage in California revealed ubiquitous presence and marked persistence to conventional treatment for both phenylpyrazole and neonicotinoid compounds Flea and tick control agents for pets are identified as potential sources of pesticides in sewage meriting further investigation and inclusion in chemical-specific risk assessments (Sadaria *et al.*, 2017).

4.4. Conclusions on environmental fate and exposure data

Sales data for ectoparasiticidal VMPs are usually not published in the public domain by MAHs, and there is no surveillance system in place in the EU/EEA that would allow the monitoring of their sales and use. Only very limited data from certain countries covering limited periods of time are publicly available. Based on estimated pet population statistics and posology only, an exemplary estimate of environmental emissions of ectoparasiticidal VMPs for cats and dogs in the EU/EEA can be calculated. The sales and emissions of active ingredient are driven more by dog population numbers than by that of cats and are largely influenced by the sale of collars, which contain greater amounts of active substance than cutaneous and oral formulations, although spot-on products and tablets are the most commonly used formulations (section 4.1). The proportion of the active substance which is actually released from the ectoparasiticidal collar to the animal and subsequently to the environment before disposal are unknown for most products, although, based on the data from Stannek *et al*. (2012), it can be assumed that more than half of the active substance remain in the collar at the time of disposal (section 4.2).

Concerning the fate of these active substances and their exposure routes into the environment, surface waters (including sediments) are likely the most important receiving compartment, since these are at the end of most of the proposed environmental pathways. It is possible that a part of a dose given to the animal will reach surface waters via WWTPs, run-off or direct exposure. This may be the case for both systemically- and locally-acting VMPs, whereby it is unclear how much active substance actually ends up in the environment, and how much (e.g. from used collars or disposed excreta) ends up in waste incineration plants or landfills. The pathways of exposure of ectoparasiticidal VMPs for cats and dogs into the terrestrial compartment are not well understood, nor are their potential effects on wildlife (e.g. the impact of hair from treated animals on bird offspring when used as nesting material or the impact of residues and metabolites of active substances in faeces and urine on terrestrial ecosystems). Direct exposure of the terrestrial compartment to dog faeces and urine is considered less relevant. However, this assumption may not hold true for regions with high populations of free-roaming cats and dogs (whose presence is significant in some regions; see section 3.1 for details) or for peri-urban ecosystems in populated areas (section 4.2). Another terrestrial exposure pathway would be the spreading of sewage sludge (section 4.2). As hardly any monitoring exists for the terrestrial compartment, it is not addressed further in this RP related to potential hazards or the risks.

The case studies on environmental monitoring data from seven geographical regions for imidacloprid and fipronil show that the situation is very heterogenous in the different regions. The European monitoring data mostly originate from measurement periods when fipronil and imidacloprid were not yet banned as ingredient of PPPs. While there are indications that the use of pet VMPs contributed to surface water concentrations of fipronil and imidacloprid at some monitoring sites, no such influence is

apparent at other sites. Not surprisingly, higher concentrations were detected at sites in tributaries during drought conditions and downstream of WWTPs, when compared to sampling sites located in water-rich rivers such as the main stream of the Danube or the Rhine. Attempts to quantify the contribution of parasiticidal VMPs for cats and dogs to the environmental concentrations in wastewater effluents and surface waters have been made. However, the related conclusions are equivocal, as the main input data to perform a robust source apportionment (i.e. detailed sales data for VMPs, biocides and PPPs) are not available. Likewise, attempts to establish exposure models have been published, although they are subject to large uncertainties due to insufficient or incomplete input data, e.g. with regard to the relevant exposure pathways or emission data.

Nonetheless, it cannot be ruled out that VMPs used in pets contribute to fipronil and imidacloprid concentrations measured in urban wastewater effluents. At the same time, it can be assumed that water bodies in the rural catchment area are more influenced by agricultural use (section 4.3).

5. Environmental hazards

Since VMPs for use in companion animals typically are exempted from a phase II ERA, as detailed in sections 1 and 2.1. , information on environmental hazards (and risks) is only rarely available from authorisation procedures of ectoparasiticidal VMPs for cats and dogs.

However, for many of the active substances within the scope of this reflection paper, comprehensive data sets on environmental hazard assessments and effects data from ERAs conducted under other legislative frameworks are available and could be used for ERAs of the ectoparasiticidal VMPs. For some active substances, environmental hazard information are even already included in the product literature of the ectoparasiticidal VMPs. Such data will not be duplicated or summarised here. The same applies to data from PBT assessments and further information on substance-related properties (e.g. potential endocrine disruptive properties). Relevant notes and a brief overview on the availability of such environmental data as well as on legislative decisions can be found in Annex I. For other substance classes, which are only used in VMPs for cats and dogs and for which only little or no environmental hazard information exist due to the provisions of the VICH GLs, other relevant publicly available information such as physicochemical properties and excretion data are summarised in Annex I.

This section focuses on outlining the most relevant environmental hazards or substance properties for exemplary substances (substance classes), to bring the measured environmental concentrations in the previous chapter into context and to facilitate the discussion in section 6.

The locally-acting substances imidacloprid and fipronil have been selected in support of the discussion of the case studies described in chapter 4.3. For these active substances, monitoring data are most abundant and non-pet VMP uses are being more and more restricted, which may, in the future, result in exposures being attributable to VMPs for companion animals with more certainty than today, as detailed in section 3.3 and 4.1.

The systemically-acting substance class of isoxazolines has been selected as their inherent chemical properties (lipophilicity, long-lasting activity) may give rise to environmental concern. Also, high sales volumes from the use in VMPs for cats and dogs can presently be assumed, with an increasing trend (see section 4.1).

Due to the nature of the use of VMPs for cats and dogs, the exposed environmental compartments are likely to be aquatic ecosystems, either directly as a result of (mainly) dogs swimming in surface water bodies or indirectly through wastewater systems. Locally, soil ecosystems may be exposed as well,

whereas exposure to pollinators is thought to be insignificant. For details on environmental exposure pathways see chapter 4.2.

Environmental hazard information for aquatic ecosystems

Environmental quality standards or protection limits can be an important source of information on environmental hazards. Depending on the underlying legislative framework (e.g. WFD, authorisation/placing on the market of PPPs, biocidal products or VMPs), quality objectives (long-term/chronic toxicity or short-term/acute toxicity) or protection goals (e.g. aquatic invertebrates, terrestrial non-target arthropods, drinking water. etc.), there are different concepts of defining the hazard levels of substances towards aquatic ecosystems. Therefore, the concentrations of a chemical in surface waters below which no unacceptable effects are expected to occur are denominated differently in certain references, for instance EQS, RAC or PNEC (see case studies in section 4.3). The emergence of new data often leads to a revision of these limits. **Table 7** gives an overview on the hazard limit values used for the evaluation of the monitoring data in section 4.3 and in further references and shows that all active substances are toxic at a very low level.

Table 7. Environmental hazard limits for aquatic ecosystems for the example substances imidacloprid, fipronil and fluralaner, as referenced in section 4.3. (monitoring data/case studies) and below.

Hazard limit	Imidacloprid	Fipronil	Fluralaner	Reference
AA-EQS[1] MAC-EQS[2]	0.0083 µg/L 0.2 µg/l	0.0007 µg/L	-	(EC, 2011; Smit *et al.*, 2015)
Draft AA-EQS[1] Draft MAC-EQS[2]	0.0024 (0.0068) µg/L 0.065 (0.057) µg/L	-	-	(SCHEER, 2021)
RAC[3]	0.009 µg/L	0.00077 µg/L	-	(Liess *et al.*, 2022)
Lowest PNEC/proposed PNEC[4]	0.0083 µg/L	0.00077 µg/L		(Liška *et al.*, 2021)
PNEC[5] (fresh water organisms)		0.012 µg/L	-	(ECHA, 2011b)
Water and sediment quality criterion[6]		0.0032 µg/L		(Bower and Tjeerdema, 2017)
PNEC[7] (surface waters)			0.00047 µg/L	(Lahr *et al.*, 2019; EMA/CVMP, 2022)

1 AA-EQS: Long-term environmental quality standard (EQS) expressed as an annual average concentration (Directive 2000/60/EC)[2] MAC-EQS: Maximum acceptable concentration-EQS based on acute ecotoxicity data aimed protecting the ecosystem from short-term concentration peaks (Directive 2000/60/EC)
[3] RAC: Regulatory acceptable concentrations used in the authorisation process of PPPs (EFSA, 2013b)
[4] PNEC: Predicted no effect concentration for the suggested 16 "Danube River Basin Specific Pollutants" (lowest PNEC) and the 10 WL substances (updated or proposed PNEC) in the Joint Danube Survey 4.
[5] PNEC: Predicted no effect concentration used within the biocidal products legal framework (as part of the EU-wide inclusion of active substances in Annex I or IA to Directive 98/8/EC)
[6] Criteria established by the Central Valley Regional Water Quality Control Board in the USA
[7] PNEC: Predicted no effect concentration from the authorisation process of a VMP for the use in food-producing animals.

Hazards of imidacloprid

The environmental hazards associated with imidacloprid are related to its function as an insecticide and with effects on the nervous system. Imidacloprid and other neonicotinoids bind to the post-synaptic nicotinic acetylcholine receptors (nAChRs) in the central nervous system of insects and other

invertebrates and thereby disrupt impulse transmission between cells. Consequently, a very high toxicity has been observed towards not only target pest organisms, but also towards other species such as aquatic invertebrates (e.g. crustaceans), pollinating insects (e.g. bees) and soil-dwelling organisms such as springtails. In order to protect especially pollinators from exposure, neonicotinoids have been banned in Europe from use as pesticides in non-closed agricultural systems. Data has shown that the most commonly used test species for aquatic toxicity to invertebrates is not as sensitive to imidacloprid toxicity when compared to aquatic arthropod species, which are species commonly found in many freshwater systems across Europe (Posthuma-Doodeman, 2008). Such findings have repeatedly led to a reduction of water quality standards.

In 2007, a literature review was carried out in the Netherlands in order to derive an environmental risk limit for imidacloprid and to derive water quality standards according to the WFD (Posthuma-Doodeman, 2008). This resulted in a Dutch AA-EQS of 0.067 µg/L and a MAC-EQS of 0.2 µg/L (Posthuma-Doodeman, 2008). In 2015, Smit *et al.* (2015) revisited and updated the review of ecotoxicological data published and concluded that the standard for long-term exposure should be lowered to 8.3 ng/L, whereas the MAC-EQS for short-term concentration peaks could be maintained at 0.2 µg/L. In autumn 2021, the European Commission' Scientific Committee on Health, Environmental and Emerging Risks (SCHEER, 2021) reviewed the EQS for imidacloprid as Priority Substance under the WFD and endorsed a lower MAC-EQS for freshwater of 0.065 µg/L (derived using a deterministic procedure) and 0.057 µg/L (derived using a probabilistic procedure), respectively. The SCHEER further endorsed a lower AA-EQS of 2.4 ng/L (deterministic) and 6.8 ng/L (probabilistic), respectively.

Environmental behaviour:

Imidacloprid was assessed by EFSA as having a high to medium mobility in soil and high solubility, being essentially stable to hydrolysis, but sensitive to photolysis (EFSA, 2008). In the studies provided for the inclusion of imidacloprid as biocidal substance in the Annex I of Directive 98/8/EC (ECHA, 2015), the following was concluded regarding environmental fate and behaviour: In open waters, imidacloprid disappears very slowly, but the disappearance time is significantly shorter when exposed to light. The average $DT_{50\text{-TOTAL SYSTEM}}$ is of 185.4 days at 12 °C. The $DT_{50\text{-WATER}}$ varied from 31.6 to 242 days at 12 °C. The mean adsorption coefficient normalised to organic carbon (K_{oc}) was 230 mL/g, i.e. a medium mobility in soil according to the McCall classification scheme. Imidacloprid has a high solubility in water (613 mg/L in water at 20 °C).

Hazards of fipronil

The environmental hazards of fipronil are similarly related to its function as an insecticide with effects on the nervous system. Fipronil blocks $GABA_A$-gated chloride channels in the central nervous system and thus prevents the uptake of chloride ions resulting in excessive neuronal stimulation and death of target and non-target insects.

The assessment report submitted for fipronil as part of the EU-wide inclusion of active substances in Annex I or IA to Directive 98/8/EC identified a PNEC for fresh water organisms of 0.012 µg/L (ECHA, 2011b). The lowest chronic no observed effect concentration (NOEC) value was found to be 0.121 µg/L derived from a spiked water test with *Chironomus riparius*. The Central Valley Regional Water Quality Control Board in the USA has published a water and sediment quality criteria report for fipronil (Bower and Tjeerdema, 2017), establishing a criterion of 3.2 ng/L based upon acute (LC_{50}) toxicity values and chronic-to-acute toxicity ratios. In the context of the Danube River Basin Specific Pollutants, a lowest PNEC value of 0.77 ng/L was established, indicating a risk to the aquatic environment (Liška *et al.*, 2021).

Environmental behaviour:

Fipronil is also sensitive to photolysis and persistent in soil and water-sediment systems. It is being classified as having a low to medium mobility and as being slightly soluble (EFSA, 2006a). In the studies provided for the inclusion of fipronil as biocidal substance in the Annex I of Directive 98/8/EC (ECHA, 2011b), the following was concluded regarding environmental fate and behaviour: In an aquatic environment, fipronil partitions into sediment showing a $DT_{50\text{-WATER}}$ of 23.13 days at 12 °C and a $DT_{50\text{-TOTAL SYSTEM}}$ of 61.69 days at 12 °C. The mean K_{oc} was 727 mL/g, i.e. a low mobility in soil according to the McCall classification scheme. Fipronil has a low solubility in water (3.78 mg/L at 20 °C and pH 6.58).

Hazards of isoxazolines

Data on the environmental hazards or the environmental behaviour of isoxazolines are scarce. As most isoxazolines are authorised as VMPs for companion animals only (and not as biocides, PPPs or VMPs for livestock, with one exception), very few studies on environmental effects or the environmental behaviour have been conducted in the frame of the respective authorisation procedures, if at all, in line with VICH GL 6 (see chapter 1). Likewise, the environmental hazards of isoxazolines have only seldom been investigated in dedicated and publicly available studies so far. However, the insecticidal and acaricidal properties of isoxazolines in combination with potential persistence and potential bioaccumulative properties (based on *n*-octanol-water partition coefficients (log K_{ow}) of ≥ 4) constitute a concern. Substance properties and data retrieved from pharmacokinetic studies conducted in dogs with afoxolaner, fluralaner, sarolaner and lotilaner prior to marketing authorisation (Kilp *et al.*, 2014; Letendre *et al.*, 2014; McTier *et al.*, 2016; Toutain *et al.*, 2017; EMA/CVMP, 2020a, 2020b, 2021b, 2021a) can be summarised as follows (for details and further references see Annex I): Isoxazolines are characterised by a high lipophilicity, with measured log K_{ow}s > 5 for fluralaner and lotilaner, and predicted log K_{ow}s of 6.7 and 3.4 for afoxolaner and sarolaner, respectively. They tend to readily distribute into tissues. Combined with a low clearance, this explains the long terminal half-life between 11 and 30 days after oral administration in dogs. With the exception of afoxolaner, which is notably transformed to water soluble metabolites, these substances are only poorly metabolised after administration, if at all. The major elimination pathway is excretion of unchanged parent compound via faeces with only a minor (afoxolaner) to negligible (sarolaner, fluralaner, lotilaner) proportion being excreted via urine.

For fluralaner, Lahr et al. (2019) defined a hazard limit of 0.47 ng/L for surface waters based on a chronic NOEC of 47 ng/L in *Daphnia magna*, which was determined in the frame of the authorisation of a VMP indicated for the treatment of the red mite (*Dermanyssus gallinae*) in poultry, to date the only use of an isoxazoline in food-producing animals in the EU/EEA (EMA/CVMP, 2022).

<u>Environmental behaviour:</u>

From the above-mentioned tailored ERA, a $DT_{50\text{-WATER}}$ between 7.7 and 8.3 days at 12 °C and $DT_{50\text{-SEDIMENT}}$ between 196.2 and 112.1 days for fluralaner was derived. The K_{oc} was in the order of 20,000 mL/g, i.e. the compound is immobile in soil according to the McCall classification scheme. Considering these findings, fluralaner has been classified as persistent/very persistent (P/vP) in soil and aerobic freshwater sediment, while it is clearly not persistent in freshwater and anaerobic freshwater sediment. Data on solubility is available from the authorisation of an ectoparasiticidal VMP for use in dogs (EMA/CVMP, 2021a), where a low solubility in water (0.1 mg/L) is reported. Data on the environmental behaviour of other isoxazolines could not be found, although it is reasonable to assume that they would show a similar environmental behaviour to fluralaner.

6. Discussion

6.1. ERA of ectoparasiticidal VMPs used in cats and dogs

The methodology of environmental risk assessment under the VMP legal framework is a function of the exposure and the toxicity of the active substance. However, for this particular exercise, the limited data available do not allow for a quantitative assessment. For this reason, the CVMP opts for a qualitative discussion below, based on expert judgement on whether the current approach laid down in VICH GL6 for the ERA of VMPs containing (ecto-)parasiticidal substances used in cats and dogs remains scientifically justified and if the use of ectoparasiticidal VMPs in cats and dogs poses a risk for the environment.

6.1.1. Exposure assessment

Use and exposure pathways

Given the proposed exposure pathways into the environment (section 4.2), manifold pathways into both the terrestrial and the aquatic compartment can be assumed, except for those leading directly into municipal surface waters such as via the washing of exposed pets and textiles. In urban areas, the different pathways of active substances to the surface water converge in a limited number of WWTPs that then discharge in a smaller number of rivers, i.e. the emission to the environment is concentrated around hotspots that collect active substances from several routes and sources. For example, the city of Madrid (metropolitan area excluded) has eight WWTPs that collect all the sewage waters from the city which are then discharged into only two rivers. It is important to note that the water flow of the receiving waters will influence the extent of the pollution, as the dilution effect will be limited in smaller rivers or in drier seasons.

The data available on the cat and dog population in the EU/EEA (section 3.1) shows that the numbers are increasing across the EU/EEA. An increase of the target population would normally lead to an increase of the total use of pets' ectoparasiticides. Nevertheless, it has to be taken into account that the pet population data available are incomplete and of low reliability, as the sources of information or the methodology followed are not mentioned in the available reports.

No EU/EEA-wide surveillance data are available on the sales or use of VMPs containing ectoparasiticidal active substances. National data for the Netherlands (section 4.1) of 2018/19 show that dogs are the main treated species by active substance tonnage, that pyrethroids and neonicotinoids are the active substances most sold and that there is a clear preference for topical treatments and collars. Globally, parasiticides (in general) for companion animals and horses account for 67% of the market share by financial value and endectocides and ectoparasiticides constitute more than 60% [section 1]). Although these figures cannot be translated into use data, this information gives an indication of the extent of the use of these substances in companion animals.

Ectoparasite infestations mostly follow a seasonal pattern that reach a maximum peak in spring and summer. In temperate climates the peak season is longer. In Mediterranean regions, the treatments applied in summer coincide with the dry season, so the dilution of discharges from WWTP into waterways is smaller.

Spot-on formulations typically require a monthly application during the at-risk season, while collars ensure a homogeneous release of active substance for 4–6 months. Most active substances used in topical formulations are poorly absorbed (section 3.2), which means that a significant part of the dose may remain on the animal's coat. When the animal is then washed after treatment, there is a possibility that a part of the active substance present on the coat will be washed off and then reach

WWTPs. The transfer of active substances to house dust, textiles, clothing or hands can also be a pathway to sewage (section 4.2).

Oral formulations (section 3.2) are effective for one to three months and the active substances need to be excreted by the animal before reaching the environment. In urban settings, faeces are generally disposed as solid waste. Urine would need to be washed to the drains to reach WWTPs.

Fate and behaviour

Data on the ability of WWTPs to remove ectoparasiticides from influents is scarce. Conventional WWTPs (section 4.2; case studies 4 and 7), however, do not seem to be able to effectively remove imidacloprid or fipronil from the influent. For permethrin, a high removal rate is reported.

Imidacloprid was assessed by EFSA (2008) as having a high to medium mobility in soil and high solubility, so, depending on its stability in WWTPs, it is unlikely to be removed by conventional WWTPs with secondary treatment. Imidacloprid is essentially stable to hydrolysis, but sensitive to photolysis (EFSA, 2008). Fipronil is also sensitive to photolysis and persistent in soil and water-sediment systems. It is classified as low to medium mobile in soil and slightly soluble (EFSA, 2006a). The isoxazoline fluralaner is poorly soluble in water and classified as persistent/very persistent (P/vP) in soil and aerobic freshwater sediment (section 5).

It is important to note that not only the properties of the three example substances described in section 5 give rise to concern. Other substances contained in ecto- and endectoparasiticidal pet VMPs such as the avermectins, milbemycins or lufenuron have similarly been classified as persistent and some (e.g. lufenuron, moxidectin) additionally as bioaccumulative (Annex I).

Presence in the environment

There are over 40 substances with ectoparasiticidal or endectocidal activity authorised in ectoparasiticidal VMPs for cats and dogs in the EU/EEA (section 3.3). Given this large number, the search for monitoring data in the present RP focused on those active substances for which, on the one hand, the use in ectoparasiticidal pet VMPs can be assumed to be very high, and on the other hand, other uses (e.g. as PPP or biocide) are being phased out or severely restricted, as in the case of imidacloprid and fipronil. In different monitoring schemes in Europe, imidacloprid and fipronil have been found in different concentrations and at different sampling sites.

In sampling points dominated by agricultural activities, the presence of imidacloprid or fipronil in surface waters can be attributed to their use in pet VMPs, PPPs and/or biocides. Nevertheless, the use and sales of imidacloprid and fipronil was prohibited for most agricultural applications in 2018 and 2014, respectively, and were, in the following years (due to transition periods), successively restricted in each Member State (Annex I). Monitoring data presented in section 4.3., however, largely originate from these transition periods. The environmental concentrations of these substances in future monitoring studies may be less influenced by agricultural activities.

In sampling points in the urban catchment area (WWTPs and downstream waterways), the presence of imidacloprid and fipronil has been confirmed by monitoring data. Imidacloprid and fipronil from the use in PPPs could originate from residues in vegetables being released to drains after washing vegetables or from excretion from consumers exposed to residues by ingestion. The emissions of imidacloprid in urban scenarios from the use in biocides is likely to be very low considering the authorised uses (traps and gels; see section 5 and Annex I). The use of these active substances in VMPs for cats and dogs can be an additional source of environmental exposure in urban areas. In measurements where imidacloprid or fipronil were detected in WWTPs, the source of the active substances (VMP, PPP or

biocide) cannot be differentiated, but the intricate route of the use in PPPs and the limited emissions from biocides indicate that the use as in VMPs for companion animals contribute to the presence in urban wastewater. Modelled data available in public literature aimed to prove the contrary, but these results were challenged by other authors highlighting shortcomings in the methodology used.

Discussion of monitoring data

Monitoring data from different regions are presented, however, for various reasons direct comparisons cannot be made. For instance, the marketing of biocides and PPPs containing fipronil and imidacloprid were not suspended simultaneously nor to the same extent in the different countries. In many cases, monitoring programmes were conducted during or shortly after the phasing-out period of the use of these substances and, in addition, all measured surface water concentrations may have been influenced by amounts originating from sources outside of the EU in some regions. In contrast to Europe, in the USA, both fipronil and imidacloprid are widely used as biocides in urban areas. Nonetheless, recent studies (Teerlink *et al.*, 2017; Perkins, Whitehead, Civil, *et al.*, 2021; Liess *et al.*, 2022) conclude that veterinary flea and tick products constitute a relevant contribution to the measured environmental concentration levels in the USA. However, knowledge gained about the behaviour of these substances in WWTPs in the USA could also be relevant for the situation in the EU, especially for areas with similar climatic conditions.

Fipronil or imidacloprid was detected in some cases only to a minor or negligible extent in large rivers such as the Danube or the Rhine. Furthermore, concentrations in sewage sludge or sediments were not assessed and general knowledge gaps exist regarding the bioavailability of fiproles and imidacloprid in water. For example, the bioavailability in sediments has not been investigated yet, as shown by Perkins *et al.* (2021), who found no studies that could distinguish between compounds freely dissolved, sorbed to solids or sorbed to dissolved solids.

It cannot be ruled out that VMPs used in pets contribute to fipronil and imidacloprid concentrations measured in urban wastewater effluents. At the same time, it can be assumed that water bodies in the rural catchment area are more influenced by agricultural use. The presence of these substances in sewage sludge is not known.

6.1.2. Effect assessment

Due to the high number of substances with ectoparasiticidal effect authorised in pet VMPs in the EU/EEA, the review of effects in the environment was focused on two active substances: imidacloprid and fipronil (due to the abundance of monitoring studies) and the substance class of isoxazolines (due to their chemical properties and increasing use).

Imidacloprid has an insecticidal effect, whereas fipronil and the isoxazolines have an insecticidal and an acaricidal effect (Section 5). All of them have a toxic effect at nervous system level to all (free-living and parasitic) arthropod species, but the sensitivity of the different species varies. As imidacloprid and fipronil have been authorised under other frameworks regulating their use as chemicals (PPPs, biocides), public assessment reports are available that inform about the toxicity of these substances to aquatic organisms. The aquatic invertebrates are the most sensitive species and the NOECs are typically in the order of decimal µg/L. Ecotoxicological data for isoxazolines is scarce, but the information available points to a higher toxicity to aquatic invertebrates with NOECs in the order of centesimal µg/L.

6.1.3. Risk assessment

The growing pet population, the frequent and repeated use of ectoparasiticides, the poor absorption by the treated animal, together with chemical properties like persistence, make it possible that residues of active substances with insecticidal and/or acaricidal effect will enter WWTPs in urban areas. This possibility is higher for those active substances with widespread use such as imidacloprid, pyrethroids or fipronil, or other substances depending on regional practices of use. WWTPs do not appear to be able to remove or degrade some active substances before discharge to surface waters, although related information is scarce for most of them. Imidacloprid was detected in effluents from WWTPs in several countries in Europe. The presence of imidacloprid in those samples can be attributed to its use in biocides, PPPs (including residues in vegetables) and pet VMPs. The contribution of pet VMPs to the total amount of imidacloprid in wastewater effluents is likely to be relevant since the exposure attributable to biocide and PPP use is considered to be low due to intricate exposure pathways to the WWTPs (PPP use) or due to application routes limiting the exposure to the environment (biocide use). The available data for pyrethroids and fipronil in effluents from WWTPs is weaker, but the wide use of these active substances makes it possible that they may also be discharged to surface waters in relevant amounts. The high inherent toxicity of the example substances imidacloprid, fipronil and fluralaner allows to anticipate environmental effects in a wide range of free-living arthropods present in aquatic environments where these substances are found in relevant concentrations. At least some of active substances that are used in VMPs likely results in discharges to surface water, adding to the multiple chemical mixtures and stressors already present. The dilution of the active substances with upstream water reduces concentrations in the affected area and, consequently, the river section affected would be larger in smaller rivers and during dry weather conditions. In densely populated areas, often several WWTPs frequently discharge into the same river, resulting in addition of adverse effects and a greater environmental impact. The presence of fipronil and imidacloprid has also been confirmed in rivers located in agricultural areas, where the contribution of VMP use to the total environmental presence of the active substances is likely to be lower than in urban areas.

On the basis of the available information, it cannot be ruled out that some ectoparasiticidal VMPs used in cats and dogs (at least at higher consumption levels) contribute to the concentrations of ectoparasiticidal substances that pose a risk to the aquatic environment in the vicinity of WWTP discharges.

6.2. Risk mitigation measures

A review of the PIs of authorised ectoparasiticidal VMPs for cats and dogs showed that the risk mitigation measures (RMMs) included are not uniform across the EU/EEA, as many products do not contain RMMs at all and, if they do, the wordings differ. In most VMPs for topical application, there are usually two types of RMM included, i.e. one referring to collars and another to spot-on products.

For collars the following (template) wording should appear*:* "<Active substance> is toxic for aquatic organisms. Remove the collar before allowing the dog to swim and before bathing the dog to avoid adverse effects on aquatic organisms". The CVMP "Reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products" (EMA/CVMP/ERAWP/409328/2010; (EMA, 2012), which is currently under revision, recommends the above wording and considers the measure in line with the current ERA guidance, i.e. the RMM is able to mitigate the exposure of the VMP to the environment and it is possible to demonstrate the effect of the proposed RMM by re-evaluating the exposure assessment with the proposed risk mitigation measures included.

For spot-on products, the following (template) wording should appear: "<Active substance> is toxic for aquatic organisms. Treated dogs should not be allowed to enter surface water for <x> hours/days after treatment, to avoid adverse effects on aquatic organisms". Typically, the duration for which access to water should be avoided is not more than 48 hours. Unless there are concerns to suggest otherwise, it is assumed that after this period release of active substance(s) from fur will be negligible. This wording is recommended in the RP mentioned above (EMA, 2012) and is considered in line with the current ERA guidance, i.e. the RMM is able to mitigate the exposure of the VMP to the environment and it is possible to demonstrate the effect of the proposed RMM. However, the RMM of keeping dogs out of the water for a 48-hour period is a generally applied precautionary measure and is not determined in the frame of a product-based scientific assessment.

The applicable CVMP "Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats" (EMEA/CVMP/EWP/005/2000; (EMA, 2021) states that "[t]esting for water stability for products intended for external use, the water stability of the formulation intended for marketing should be demonstrated […]. The impact of exposure to […] on the acaricidal/repellent effect should be evaluated […]. Alternatively, data on the concentration time course of the active substance in the fur after single/repeated washing after treatment can be provided. If the water stability of the product intended for marketing could not be demonstrated […] the warning should always be included in the SPC and package leaflet to avoid frequent swimming or shampooing the animal, or to remove an antiparasitic collar beforehand because the maintenance of effectiveness of the product in these cases has not been tested".

A review of PIs showed that the efficacy of the treatment (spot-on and collars) after washing the animal has not been investigated in detail in most cases. For some spot-on VMPs containing fipronil[5], one weekly immersion has been demonstrated to reduce the persistent efficacy against fleas during one week, other products state that water immersion repeated on two occasions post treatment does not affect the adulticidal efficacy against fleas nor the efficacy related to the prevention of the development of flea eggs into adult flea. The impact of water immersion or shampooing on the efficacy against tick infestation was not investigated. Some spot-on VMPs containing imidacloprid mention that if the animal bathes 48 hours after application, the VMP continues being effective.

The PIs of many deltamethrin-containing collars[6] state that the occasional contact with water does not reduce the effectiveness, but it is recommended that animals are not (bathed or) allowed to swim for the first five days after treatment. These statements clarify that, for some active substances and presentations, the efficacy for some indications is maintained under specific conditions (e.g. immersion in water). Nevertheless, it must be taken into account that maintaining the efficacy in topical formulations does not necessarily mean that there is no release of the active substance into the water. In addition, washing an animal may result in a higher release of active substance than mere immersion.

It is also important to note that most of product information reviewed for such VMPs included data on the effects of contact with water on the efficacy of the treatment, albeit the PI usually contains an environmental warning advising not to allow treated animals to enter surface water for 48 hours after treatment, as recommended in the above-mentioned RP on RMMs (EMA, 2012). Nevertheless, for efficacy reasons, the PI of some VMPs recommends extending this period to 5 days. Regarding

[5] Numerous national authorisations in the EU/EEA (e.g. Alfamed, Amflee, Bob Martin, Chanonil, Diptron, Dixie, Duoflect, Duowin, Ectoline, Effinol, Effipro, Effitix, Eliminall, Fipralone, Fiprex, Fipro-activ, Fiprocare, Fiprocat, Fiproclear, Fiprodog, Fiprofen, Fiprofile, Fiprokil, Fipromax, Fipromedic, Fipron, Fiprosoin, Fiprospot, Fiprotc, Fiproxil, Fleanil, Flevox, Flick, Frontline, Fyperix, Fypryst, Lifronil, Norspot, Perfikan, Pestigon, Safepet, Scorvet, Stop-X, Strectis, Vetocanins, Zeronil)

[6] Numerous national authorisations in EU/EEA (e.g. Canishield, Clexon, Deltatic, Flyban Merlin, Prevendog, Reflecto, Scalibor). English summaries of product characteristics (SPCs) available at https://mri.cts-mrp.eu/portal/home?domain=v

environmental information and disposal advice, the PIs reviewed for spot-on products and collars contain appropriate information and advice. Although the impact of excreta from treated pets on the terrestrial compartment have not been studied so far, consideration should be given to the development of new RMMs for systemically-acting VMPs regarding the collection and disposal of faeces from treated animals considering known metabolism and excretion pathways as well as the toxicity, inherent chemical properties (lipophilicity, long-lasting activity) and structural characteristics of the active substances involved.

Assuming that there is a relevant emission of ectoparasiticidal substances into the environment and accepting the high toxicity these substances pose to aquatic invertebrates, additional (and appropriate) risk mitigation and communication measures may be considered in order to limit the environmental exposure as much as possible. The following are suggested:

- Raising awareness on the environmental hazards these VMPs may pose among veterinarians and pet owners, but also among pet supply sellers, pharmacists, pet associations or operators of animal shelters.
- An improved removal efficiency of active substances in WWTPs may help to reduce the environmental exposure and thereby reduce the risk for the aquatic environment.
- Avoiding overuse, i.e. apply the correct dose and this only when necessary for treatment and prevention and during the at-risk situations that will vary depending on climatic and husbandry conditions.
- Avoiding off-label, i.e. use combination products containing multiple active substances only as indicated in the PI (use for mixed infestations/infections only).
- Using of disposable gloves when recommended for the application followed by disposal with solid waste.
- Applying a holistic treatment concept, i.e. the use of ectoparasiticidal VMPs should only be seen as one part of an overall concept of ectoparasite management to protect public as well as animal health and to ensure animal welfare. The use of VMPs may also be reduced by implementing a variety of non-medical preventive measures.
- In the interest of a "One Health" approach, the stray and feral cat and dog population should also be considered in a holistic treatment concept (Overgaauw et al., 2020).

6.3. Possible monitoring options

The analysis of monitoring data on imidacloprid and fipronil levels from several studies performed in different countries and regions and the analysis of samples from WWTPs and surface waters demonstrate that, at some sites, there is an indication that the use of pet VMP contributed to the concentrations found in these samples. For most sites, however, the data do not allow direct conclusions on the environmental exposure caused by specific VMPs for cats and dogs. On the other hand, it must be acknowledged that, particularly in urban areas, exceedances of water quality standards have been observed, for which VMPs for cats and dogs cannot be ruled out as (part of) the cause. That being said, the monitoring data presented provide a good illustration of the complexity of the situation and contribute valuable information on most relevant exposure pathways. The studies also illustrate very well that this is a cross-regional, cross-border and cross-sectoral issue (e.g. involving "internet trade" and "multi-use-substances") and the importance of discussing

ectoparasiticidal VMPs within the "One Health"[7] concept, as also outlined by Domingo-Echaburu *et al.* (2021) or Mahefarisoa *et al.* (2021).

Until recently, imidacloprid was the only active substance contained in ectoparasiticidal VMPs for cats and dogs on the EU surface water WL. Fipronil was included in the 4th surface water WL due to its aquatic toxicity and persistence (JRC, 2022). The design of future monitoring programs for multiple-use substances and the interpretation of data should also consider the use of such VMPs and that general knowledge gaps exist regarding the bioavailability such substances in water.

In addition, specific ad-hoc monitoring studies for specific (ecto-)parasiticidal active substances used in VMPs for cats and dogs are needed and should be carried out at potential hotspots, for example near WWTP effluents. Considering the low dilution factor in small water bodies, monitoring data from swimming ponds and swimming lakes as well as public dog bathing areas would also be of high interest. Given the high adsorption properties of many active substances, such targeted measurement programs should also include sediments and sewage sludge, as knowledge gaps exist as to whether such compounds are freely dissolved, sorbed to solids or sorbed to dissolved solids. The impact of excreta from treated pets on the terrestrial compartment, for example in peri-urban ecosystems, should also be part of reflections on future measurement programs and scientific studies.

6.4. Recommendations

Some data gaps exist in respect of the currently available knowledge on potential environmental risks for specific ectoparasiticidal substances. Therefore, it is still difficult to advise users on which substances, product types or routes of application would be less harmful for the environment than others. A better regulation of the sale of these products (e.g. advertisement control) or the consideration of environmental safety when assigning the prescription status may be beneficial, as this would motivate pet owners and caretakers to have veterinarians prescribe tailored treatment plans suited to the specific needs of the individual companion animal or the stray animal populations in a specific region. Rules for the prescription status of VMPs are laid down in Article 34 of Regulation (EU) 2019/6 (section 3.2).

At this point, raising awareness appears to be the recommendation that is the most easily implemented. Promoting the prudent use of veterinary medicinal products—from the perspective of efficacy and environmental sustainability—could significantly reduce (potential) risks posed by these products to the environment at source. Existing environmental hazard information should also be declared in a harmonised way in the product literature of all VMPs for cats and dogs.

The RMM specified in the PI of ectoparasiticidal collars (i.e. removal of collar before getting in contact with water) appears to be valid and useful. Nevertheless, it must be kept in mind that the active substance present in the fur of the animal could still be released when the animal is washed or swims in surface waters with the collar removed. Consequently, the RMM is not necessarily eliminating the risks of environmental emissions, but reducing them.

The RMM specified for spot-on VMPs usually recommends that animals should not enter surface waters 48 hours following the treatment. There is no temporal restriction for washing treated animals for environmental safety reasons, during which the release could be higher. The assumption of the environmental safety of the 48-hour period as a general precaution does not appear to be based on a product-specific scientific assessment and it is doubtful if it applies to all active substances and all formulations, especially considering that, for some VMPs, a longer period is recommended to maintain efficacy.

[7] https://www.oie.int/en/what-we-do/global-initiatives/one-health/

Although the impact of excreta from treated pets on the terrestrial compartment has not been studied so far, consideration should be given to the development of new RMMs for systemically-acting VMPs regarding the collection and disposal of faeces from treated animals, considering known metabolism and excretion pathways as well as the toxicity, inherent chemical properties (lipophilicity, long-lasting activity) and structural characteristics of the active substances involved.

7. Conclusions

This RP aims to give an overview of the current situation in the EU/EEA regarding the use of ectoparasiticidal VMPs for cats and dogs and the active substances contained therein, in order to evaluate whether the current approach for the ERA of such products remains scientifically justified. To that effect, the amounts and potential routes of environmental exposure, including an estimation of the environmental risks resulting from the use of ectoparasiticidal VMPs in cats and dogs, are analysed in more detail, in addition to the applicability of additional RMMs and possible monitoring options.

Current situation regarding the cat and dog population and ectoparasiticidal VMPs

Pet ownership has steadily increased across Europe over the past decades and this trend is clearly continuing, albeit there are no robust data on the overall pet population in the EU/EEA. Other details on the cat and dog population gathered at EU level are scarce as well, including the number of owned and non-owned companion animals (including stray and feral animals as well as those in shelters) or information on husbandry conditions (free-roaming or not), which might influence the use-patterns and the exposure of the environment to ectoparasiticidal substances.

A thorough overview of ecto- and endectoparasiticidal VMPs authorised in the EU/EEA for cats and dogs and related active substances is presented, showing that the number of available ectoparasiticidal VMPs for companion animals has significantly increased in recent years (with an increasing trend), which in turn confirms their economic value for the pharmaceutical animal health sector. It can be assumed that, until recently, the market for ectoparasiticidal VMP for cats and dogs was dominated by locally-acting spot-on products followed by collars and sprays. It can also be assumed that, since the mid-2010s, systemic treatments have been increasingly sold and applied. These assumptions are supported by limited data available in the public domain. There are clear trends towards the development and introduction of (i) formulations providing long-lasting activity; (ii) systemically-acting ectoparasiticidal VMPs that can be administered topically and orally; and (iii) combination products for the concurrent treatment and control of a variety of ecto- and endoparasites. The substance class, which is most prominently used in these developments, is the class of isoxazolines, albeit older molecules and formulations are still being used, presumably due to their low cost. For old products, there are large differences in the palette of approved VMPs within the EU/EEA, both in terms of pharmaceutical form and in terms of active substances included. The prescription status and distribution channels for pet VMPs with ecto- and endectoparasiticidal activity vary greatly within the EU/EEA.

Current ERA approach

Due to the absence of surveillance data, no conclusions can be drawn from the presented authorisation numbers about the sales of specific VMPs or the environmental emissions of individual active substances. However, based on the above-mentioned significant market share of parasiticides for companion animals in the animal health sector and on the steadily increasing pet population numbers in Europe, it may be possible that the environmental exposure of these substances from the use of ectoparasiticidal VMPs in cats and dogs is not negligible, as is currently assumed in VICH GL 6. Further

research, for example monitoring for active substances solely used in pet VMPs, could provide a better understanding of the issue. Nevertheless, based on the data currently available, it appears that the validity of the assumption (i.e. that the environmental exposure from the use of VMPs in companion animals can be considered as negligible) is open to question.

Therefore, the CVMP considers that, for certain companion animal VMPs, the current approach to stop the ERA in phase I should be revisited.

Environmental risks

Regarding the environmental exposure of active substances resulting from the use of ectoparasiticidal VMPs in cats and dogs, surface waters (including sediments) are possibly the most important receiving compartment, since most exposure pathways end up there. This may be the case for both systemically- and locally-acting VMPs. Environmental exposure pathways into the terrestrial compartment and potential impacts on wildlife have not yet been quantified (e. g. relevance of animal excreta in peri-urban ecosystems of populated areas which are not connected to urban sewage systems) or understood (e.g. potential impact of dog hair in bird nests and subsequent exposure of nestlings). Future evaluations of protection goals might go beyond the impact on aquatic arthropods.

Although spot-on products and tablets are the most commonly used formulations, the amount of active substances used are largely influenced by the sale of collars, which contain greater amounts of active substance than cutaneous and oral formulations, although the amounts actually released from the collars to the animal and subsequently to the environment before disposal are unknown. This needs to be reflected, when authorising products and developing RMMs. Similar considerations should be taken into account, when estimating environmental exposure based on cat and dog population numbers. With comparably large populations, the actual volume of active substance sales is more influenced by the use in dogs than by use in cats. Hazard data and PBT assessments exist for many older active substances due to their use in other frameworks or in food-producing animals. Environmental data are scarce for newly developed substances that have only recently entered the VMP market and are only used in companion animals (e.g. isoxazolines), in line with the provisions of VICH GLs.

Information on environmental hazards and environmental behaviour presented for three exemplary substances in this RP shows that all active substances contained in ectoparasiticidal VMPs for cats and dogs are toxic to the environment at very low levels. Knowledge gaps exist predominantly for those substances, which are only authorised in VMPs for companion animals, i.e. isoxazolines. A full product-based ERA for specific compartments or target species is not yet possible, because (i) input data, models and strategies for assessing environmental exposure still need to be elaborated; and (ii) the knowledge gaps specified above on sales and or market penetration data as well as missing environmental fate and effects data, especially for novel substance classes.

Therefore, at present, it is not possible to elaborate further on environmental risks arising from the use of individual products and substances with evidence or reasonable suspicion and, as a consequence, to rank such products according to their environmental risks, neither to generate substance-specific RMMs. It is thus recommended to address those knowledge gaps. In the meantime, VICH GL 6 provides the option to apply the "*however clause*" and to request for adequate, targeted environmental data in case of a well-justified environmental concern.

Risk mitigation measures

The currently recommended RMMs for ectoparasiticidal collars and spot-on VMPs are able to mitigate the exposure of the active substances in the environment, though some aspects may require re-evaluation. Until the above-mentioned knowledge gaps are filled, it is therefore important to be

considerate when using such VMPs. This specifically includes raising awareness on the environmental hazards that such products may pose, as well as emphasizing the importance of seeking advice on individually tailored treatment plans to avoid overuse or off-label use. The importance of following recommendations for correct use as described in the product literature should further be emphasised. The use of VMPs may also be reduced by implementing a variety of non-medical preventive measures.

The use of ectoparasiticidal VPMs for cats and dogs should be seen as part of an overall concept for ectoparasite management and control in order to protect public and animal health as well as animal welfare. The establishment of treatment plans tailored to the needs of the individual animal or a stray dog or cat population with veterinary advice is thereby an essential part of such an overall concept. Prudent use from the efficacy and user safety perspective need not be in conflict with prudent use from the environmental perspective.

Monitoring options

Considering that (i) the bans restricting the use of active substances such as imidacloprid and fipronil in PPPs and biocides have not yet been fully implemented; (ii) that pet VMPs will be a significant source of these substances in the future; and (iii) that for these substances the removal efficiencies in WWTPs are still poor, the CVMP supports the continuation of monitoring environmental concentrations of parasiticides used in cats and dogs. The design of future monitoring programs for multiple-use substances and the interpretation of data should consider the use of such VMPs and that general knowledge gaps exist regarding the bioavailability of such substances in water.

In addition, specific ad-hoc monitoring studies carried out at potential hotspots in urban catchment for specific (ecto-)parasiticidal active substances used in VMPs for cats and dogs are needed. Such targeted measurement programs should include sediments and sewage sludge. To support monitoring by environmental managers and the research community, marketing authorisation holders are encouraged to share details on analytical methods (and standards). The impact of excreta from treated animals on the terrestrial compartment, for example in urban and peri-urban ecosystems, should also be part of reflections on future measurement programs and scientific studies.

8. Abbreviations

4JDS	Fourth Joint Danube Survey
AA-EQS	Annual average concentration EQS
ACh	Acetylcholin
AChE	Acetylcholinesterase
ADME	Absorption, distribution, metabolism, and excretion
AS	Active substance
ATCvet	Anatomical Therapeutic Chemical classification system for veterinary medicinal products.
BCPC	British Crop Production Council
CA	Competent autority
CAS	Chemical Abstract Services
CMDv	Co-ordination Group for Mutual Recognition and Decentralised Procedures (Veterinary)
CMR	Carcinogenic, mutagenic and reprotoxic
CVMP	Committee for Veterinary Medicinal Products
DT_{50}	Degradation half-life or period required for 50 percent dissipation/degradation
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECHA	European Chemicals Agency
ED	Endocrine disruptor
EEA	European Environment Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EQS	Environmental Quality Standard
ERA	Environmental risk assessment
ERAWP	Environmental risk assessment working party
ESCCAP	European Scientific Counsel Companion Animal Parasites
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
FEDIAF	European Pet Food Industry Federation
FIDIN	Fabrikanten Importeurs Diergeneesmiddelen Nederland (branch association of veterinary pharmaceutical industry in the Netherlands)
FOI	Freedom of information
GL	Guideline
HMA	Heads of Medicines Agencies

ICPDR	International Commission for the Protection of the Danube River
IGR	Insect growth regulator
K_{oc}	Organic carbon normalised distribution coefficient
Log K_{ow}	Logarithm of the *n*-octanol-water partition coefficient (K_{ow})
LoQ	Limit of quantification
MAC-EQS	Maximum acceptable concentration EQS
MAH	Marketing authorisation holder
Mio	Million
MRIv	Veterinary MRIndex
NCA	National competent authority
OJ	Official Journal of the European Union
OTC	Over-the-counter (non-prescription)
PNECs	Predicted no effect concentrations
PBT	Persistent, bioaccumulative and toxic
PI	Product information
PK	Pharmacokinetics
POM	Prescription-only medicine
PPP	Plant protection product
PT	Product-type (under the Biocidal Products Regulation (EU 528/2012)
RBSP	River Basin Specific Pollutants
RP	Reflection Paper
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment)
SPC (SmPC)	Summary of product characteristics
UPD	Union Product Database (on all authorised veterinary medicines in the EU/EEA)
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.
VMD	United Kingdom Veterinary Medicines Directorate
VMP	Veterinary medicinal product
vB	Very bioaccumulative
vP	Very persistent
WFD	Water Framework Directive (Directive 2000/60/EC)
WHO	World Health Organisation
WWTPs	Wastewater treatment plants

9. References

Anthe, M., Valles-Ebeling, B., Achtenhagen, J., Arenz-Leufen, M., Atkinson, J., Starp, M. and Corsing, C. (2020) 'Development of an aquatic exposure assessment model for Imidacloprid in sewage treatment plant discharges arising from use of veterinary medicinal products', *Environmental Sciences Europe*, 32(1). doi:10.1186/s12302-020-00424-4.

Baltussen, J.J.M. (2018) 'Onderzoek naar biociden in effluenten van rwzi ' s najaar 2017 (deel 1)', *BACO-adviesbureau BV*, 2017(deel 1), p. 45.

Baneth, G., Thamsborg, S.M., Otranto, D., Guillot, J., Blaga, R., Deplazes, P. and Solano-Gallego, L. (2016) 'Major Parasitic Zoonoses Associated with Dogs and Cats in Europe', *Journal of Comparative Pathology*, 155(1), pp. S54–S74. doi:10.1016/j.jcpa.2015.10.179.

Bäumer, W. and Baynes, R. (2021) 'Surface distribution of pyrethroids following topical application to veterinary species: Implications for lateral transport', *Journal of Veterinary Pharmacology and Therapeutics*, 44(1). doi:10.1111/jvp.12907.

Beugnet, F. and Franc, M. (2012) 'Insecticide and acaricide molecules and/or combinations to prevent pet infestation by ectoparasites', *Trends in Parasitology*, 28(7), pp. 267–279. doi:10.1016/j.pt.2012.04.004.

Bigelow Dyk, M., Liu, Y., Chen, Z., Vega, H. and Krieger, R.I. (2012) 'Fate and distribution of fipronil on companion animals and in their indoor residences following spot-on flea treatments', *Journal of Environmental Science and Health, Part B*, 47(10), pp. 913–924. doi:10.1080/03601234.2012.706548.

Bower, J.C. and Tjeerdema, R.S. (2017) 'Water and Sediment Quality Criteria Report for Fipronil', (March). Available at: waterboards.ca.gov/centralvalley/water_issues/tmdl/central_valley_projects/central_valley_pesticides/criteria_method/fipronil/pest_tmdl_bpa_fipronil_rpt.pdf.

Brianti, E., Falsone, L., Napoli, E., Prudente, C., Gaglio, G. and Giannetto, S. (2013) 'Efficacy of a combination of 10% imidacloprid and 4.5% flumethrin (Seresto®) in slow release collars to control ticks and fleas in highly infested dog communities', *Parasites and Vectors*, 6(1), pp. 1–8. doi:10.1186/1756-3305-6-210.

Broom, D.M. (2017) 'Animal Welfare in the European Union - Study PE 583.114', *European Parliament [online]*. Available at: https://www.europarl.europa.eu/thinktank/en/document/IPOL_STU(2017)583114.

CALLISTO (2014) 'CALLISTO (Companion Animals multisectoriaL interprofessionaL Interdisciplinary Strategic Think tank On zoonoses) Project - Final Report'. Available at: https://cordis.europa.eu/project/id/289316/reporting (Accessed: 28 March 2022).

Case, K.M., Vega, N.M., Gupta, R.C., Lasher, M.A. and Canerdy, T.D. (2016) 'Safety evaluation of parastar® plus in dogs and assessment of transferable residue of fipronil and cyphenothrin from dogs to humans', *Frontiers in veterinary science*, 3, pp. 89–89. doi:10.3389/fvets.2016.00089.

Cauvin, A.L. (2020) 'Is chronic parasiticide exposure a risk?', *Veterinary Record*, 186(8), pp. 252–253. doi:10.1136/vr.m728.

Cryder, Z., Greenberg, L., Richards, J., Wolf, D., Luo, Y. and Gan, J. (2019) 'Fiproles in urban surface runoff: Understanding sources and causes of contamination', *Environmental Pollution*, 250, pp. 754–761. doi:10.1016/j.envpol.2019.04.060.

Diepens, N.J., Belgers, D., Buijse, L. and Roessink, I. (2023) 'Science of the Total Environment Pet dogs transfer veterinary medicines to the environment', *Science of the Total Environment*, 858(October 2022), p. 159550. doi:10.1016/j.scitotenv.2022.159550.

Domingo-Echaburu, S., Lertxundi, U., Boxall, A.B.A. and Orive, G. (2021) 'Environmental contamination by pet pharmaceuticals: A hidden problem', *Science of the Total Environment*. doi:10.1016/j.scitotenv.2021.147827.

Eads, D.A., Biggins, D.E., Bowser, J., Mcallister, J.C., Randall, L., Childers, E., Livieri, T.M., Painter, C. and Krank, L.S. (2018) 'RESISTANCE TO DELTAMETHRIN IN PRAIRIE DOG (CYNOMYS LUDOVICIANUS) FLEAS IN THE FIELD AND IN THE LABORATORY', 54(4), pp. 745–754. doi:10.7589/2017-10-250.RESISTANCE.

EC (2011) 'Guidance Document No. 27 Technical Guidance For Deriving Environmental Quality Standards', *Common Implementation Strategy for the Water Framework Directive (2000/60/EC)*. Available at: https://ec.europa.eu/environment/water/water-framework/facts_figures/guidance_docs_en.htm.

EC (2019) 'Communication from the Commission to the European Parliament, the Council, and the European Economic and Social Committee: European Union Strategic Approach to Pharmaceuticals in the Environment', *COM(2019) 128 final*. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52019DC0128.

ECHA (2008) 'Assessment Report Indoxacarb Product-type 18 (insecticide, acaricide and product to control other arthropods)', *European Chemicals Agency [online]*. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/64/PT18 (Accessed: 27 December 2021).

ECHA (2010) 'Assessment Report Spinosad - Product-type 18 (insecticides , acaricides and products to control other arthropods)', *European Chemicals Agency [online]*. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/49/PT18.

ECHA (2011a) 'Assessment Report Deltamethrin Product-type 18 (insecticide, acaricide and product to control other arthropods)', *European Chemicals Agency [online]*. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/24/PT18.

ECHA (2011b) 'Assessment Report Fipronil Product-type 18 (insecticides, acaricides and products to control other arthropods)', *European Chemicals Agency [online]*. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/33/PT18.

ECHA (2012) 'Pyriproxyfen Product-type 18 (Insecticides, acaricides and products to control other arthropods)', *European Chemicals Agency [online]*. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/61/PT18.

ECHA (2014a) 'Assessment Report Dinotefuran - Product-type 18 (insecticide, acaricide and product to control other arthropods)', *European Chemicals Agency [online]*. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1293/PT18.

ECHA (2014b) 'Assessment Report Permethrin - Product-type 18 (insecticide, acaricide and product to control other arthropods)', *European Chemicals Agency [online]*. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1342/PT18.

ECHA (2014c) 'Assessment Report Permethrin - Product-type 8 (Wood Preservative)', *European Chemicals Agency [online]*. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1342/PT08.

ECHA (2015) 'Assessment Report Imidacloprid - Product-type 18 (insecticide, acaricide and product to control other arthropods) (revised version)', *European Chemicals Agency [online]*. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/37/PT18.

ECHA (2016) 'Assessment Report S-Methoprene - Product-type 18 (insecticide, acaricide and product to control other arthropods) updated June 2016', *European Chemicals Agency [online]*. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-

/disas/factsheet/1386/PT18.

EFSA (2006a) 'Conclusion regarding the peer review of the pesticide risk assessment of the active substance - fipronil', *EFSA Journal*, 65, pp. 1–110. doi:10.2903/j.efsa.2008.145r.

EFSA (2006b) 'Conclusion regarding the peer review of the pesticide risk assessment of the active substance diazinon', *EFSA Journal*, 4(8), p. 85r. doi:10.2903/j.efsa.2006.85r.

EFSA (2006c) 'Conclusion regarding the peer review of the pesticide risk assessment of the active substance trichlorfon', *EFSA Journal*, 4(6), p. 76r. doi:10.2903/j.efsa.2006.76r.

EFSA (2008) 'Conclusion regarding the peer review of the pesticide risk assessment of the active substance imidacloprid', *EFSA Journal*, 6(7), pp. 1–120. doi:10.2903/j.efsa.2008.145r.

EFSA (2010) 'Conclusion on the peer review of the pesticide risk assessment of the active substance fenoxycarb', *EFSA Journal*, 8(12). doi:10.2903/j.efsa.2010.1779.

EFSA (2013a) 'Conclusion on the peer review of the pesticide risk assessment for bees for the active substance fipronil', *EFSA Journal*, 11(5), pp. 1–51. doi:10.2903/j.efsa.2013.3158.

EFSA (2013b) 'Conclusion on the peer review of the pesticide risk assessment for bees for the active substance fipronil', *EFSA Journal*. doi:10.2903/j.efsa.2013.3158.

EFSA (2014) 'Conclusion on the peer review of the pesticide risk assessment for aquatic organisms for the active substance imidacloprid', *EFSA Journal*, 12(10), p. 3835. doi:10.2903/j.efsa.2014.3835.

EFSA (2018a) 'Draft Renewal Assessment Report DELTAMETHRIN Volume 1 (prepared according to the Commission Regulation (EU) N° 1107/2009)', *[online]*. Available at: https://www.efsa.europa.eu/sites/default/files/consultation/consultation/Deltamethrin.zip (Accessed: 27 December 2021).

EFSA (2018b) 'Peer review of the pesticide risk assessment of the active substance indoxacarb', *EFSA Journal*, 16(1), pp. 1–29. doi:10.2903/j.efsa.2018.5140.

EFSA (2018c) 'Peer review of the pesticide risk assessment of the active substance spinosad', *EFSA Journal*, 16(5). doi:10.2903/j.efsa.2018.5252.

EFSA (2019) 'Peer review of the pesticide risk assessment of the active substance pyriproxyfen', *EFSA Journal*, 17(7). doi:10.2903/j.efsa.2019.5732.

EFSA (2021) 'Reasoned opinion on the toxicological properties and maximum residue levels for propoxur', *EFSA Journal*, 19(1), pp. 1–16. doi:10.2903/j.efsa.2021.6374.

EMA/CVMP (1998) 'AMITRAZ (Cattle and sheep) SUMMARY REPORT (2)', *EMEA/MRL/330/97-FINAL*.

EMA/CVMP (2019) *EPAR Longrange*, *[Online]*. Available at: https://www.ema.europa.eu/en/medicines/veterinary/EPAR/longrange (Accessed: 23 January 2022).

EMA/CVMP (2020a) *EPAR NexGard*, *[online]*. Available at: https://www.ema.europa.eu/en/medicines/veterinary/EPAR/nexgard (Accessed: 27 December 2021).

EMA/CVMP (2020b) *EPAR Simparica*, *[online]*. Available at: https://www.ema.europa.eu/en/medicines/veterinary/EPAR/simparica (Accessed: 27 December 2021).

EMA/CVMP (2021a) *EPAR Bravecto*, *[online]*. Available at: https://www.ema.europa.eu/en/medicines/veterinary/EPAR/bravecto (Accessed: 21 December 2021).

EMA/CVMP (2021b) *EPAR Credelio*, *[online]*. Available at: https://www.ema.europa.eu/en/medicines/veterinary/EPAR/credelio (Accessed: 21 December 2021).

EMA/CVMP (2022) 'EPAR Exzolt', *[online]*. Available at:

https://www.ema.europa.eu/en/medicines/veterinary/EPAR/exzolt (Accessed: 30 March 2022).

EMA (2000) 'VICH GL6 Environmental impact assessment (EIAS) for veterinary medicinal products - Phase I', *CVMP/VICH/592/98-FINAL*.

EMA (2004) 'VICH GL38 Environmental impact assessments for veterinary medicinal products - Phase II', *CVMP/VICH/790/03-FINAL*.

EMA (2012) 'Reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products', *EMA/CVMP/ERAWP/409328/2010*.

EMA (2016) 'Guideline on environmental impact assessment for veterinary medicinal products in support of VICH guidelines GL6 and GL38', *EMA/CVMP/ERA/418282/2005-Rev.1-Corr.*

EMA (2020) 'Concept paper for the development of a reflection paper on the environmental risk assessment for parasiticide veterinary medicinal products used in companion animals', *EMA/CVMP/ERA/55512/2020*.

EMA (2021) 'Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats', *EMEA/CVMP/EWP/005/2000-Rev.4*.

EMA (2022a) 'Draft guideline on the application of Article 34 of Regulation (EU) 2019/6', *[online]*. Available at: https://www.ema.europa.eu/en/guidance-application-article-34-regulation-eu-2019-6-prescription-status.

EMA (2022b) *European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)*, *[online]*. Available at: https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/european-surveillance-veterinary-antimicrobial-consumption-esvac (Accessed: 30 March 2022).

ESCCAP (2022) *Control of Ectoparasites in Dogs and Cats*, *ESCCAP - European Scientific Counsel Companion Animal Parasites*. Available at: https://www.esccap.org/uploads/docs/mjy50wev_0720_ESCCAP_Guideline_GL3_v9_1p.pdf.

Fabrega, J. and Carapeto, R. (2020) 'Regulatory review of the environmental risk assessment of veterinary medicinal products in the European Union, with particular focus on the centralised authorisation procedure', *Environmental Sciences Europe*, 32(1). doi:10.1186/s12302-020-00374-x.

FAO (2017) 'FAO Specifications and Evaluations for Agricultural Pesticides for PROPOXUR', *Joint FAO/WHO Meeting on Pesticide Specifications (JMPS)*. Available at: http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/ps-new/en/.

FEDIAF (2020) 'FEDIAF Facts & Figures 2020', *The European Pet Food Industry*. Available at: https://www.fediaf.org/images/FEDIAF_Facts_and_Figures_2020.pdf.

De Frenne, P., Cougnon, M., Janssens, G.P.J. and Vangansbeke, P. (2022) 'Nutrient fertilization by dogs in peri-urban ecosystems', *Ecological Solutions and Evidence*, 3(1), pp. 1–9. doi:10.1002/2688-8319.12128.

Gooijer, Y., Hoftijser, G., Lageschaar, L., Oerlemans, A., Scheepers, P., Kivits, C., Duyzer, J., Gerritsen-Ebben, M., Figueiredo, D., Huss, A., Krop, E., Vermeulen, R., van den Berg, F., Holterman, H., Jacobs, C., Kruijne, R., Mol, J., Wenneker, M., van de Zande, J. and Sauer, P. (2019) 'Research on exposure of residents to pesticides in the Netherlands (Onderzoek Bestrijdingsmiddelen en Omwonenden)', *Utrecht University*, p. 381. Available at: https://research.wur.nl/en/publications/research-on-exposure-of-residents-to-pesticides-in-the-netherland (Accessed: 1 April 2022).

Guldemond, A., Gommer, R., Leendertse, P. and van Oers, K. (2019) 'Koolmezensterfte en buxusmotbestrijding: Pesticidenbelasting bij jonge koolmezen', (Clm), pp. 1–55. Available at: https://www.clm.nl/publicatie/173/18.

JRC (2020) 'Selection of substances for the 3rd Watch List under the Water Framework Directive -',

Publications Office of the European Union, Joint Research Centre (JRC). doi:10.2760/194067.

JRC (2022) 'Selection of substances for the 4thrd Watch List under the Water Framework Directive', *Publications Office of the European Union, Joint Research Centre (JRC)*. doi:10.2760/01939.

Kilp, S., Ramirez, D., Allan, M.J., Roepke, R.K. and Nuernberger, M.C. (2014) 'Pharmacokinetics of fluralaner in dogs following a single oral or intravenous administration', *Parasites & Vectors*, 7(1), p. 85. doi:10.1186/1756-3305-7-85.

Krieger, R. (ed.) (2010) *Hayes' Handbook of Pesticide Toxicology*. Third Edit. Elsevier. doi:10.1016/C2009-1-03818-0.

de la Casa-Resino, I., Villegas Grondona, J.M., Puig Infante, A., Haro Castuera, A., Bartolomé Rodríguez, A., Herrera Hernández, E.M., Rubio, C.F., Caixach, J. and Carapeto García, R. (2022) 'Residues of imidacloprid in surface water treatment plants and watercourses in Spain: are Veterinary Medicinal Products (VMPs) a significant source of emission?', *Spanish Agency of Medicines and Medical Devices (AEMPS)*. Available at: https://www.aemps.gob.es/publicaciones/publica/docs/Imidacloprid.pdf.

Lahr, J., Moermond, C., Montforts, M., Derksen, A., Bondt, N., Puister-Jansen, L., de Koeijer, T. and Hoeksma, P. (2019) 'Diergeneesmiddelen in het milieu huidige kennis (Rapport 2019-26)', *STOWA rapport (nummer 2019-26)*. Available at: https://www.stowa.nl/publicaties/diergeneesmiddelen-het-milieu-een-synthese-van-de-huidige-kennis.

Letendre, L., Huang, R., Kvaternick, V., Harriman, J., Drag, M. and Soll, M. (2014) 'The intravenous and oral pharmacokinetics of afoxolaner used as a monthly chewable antiparasitic for dogs', *Veterinary Parasitology*, 201(3–4), pp. 190–197. doi:10.1016/j.vetpar.2014.02.021.

Liess, M., Liebmann, L., Lück, M., Vormeier, P., Weisner, O., Foit, K., Knillmann, S., Schäfer, R.B., Schulze, T., Krauss, M., Brack, W., Reemtsma, T., Halbach, K., Link, M., Schreiner, V.C., Schneeweiss, A., Möder, M., Weitere, M., Kaske, O., von Tümpling, W., Gunold, R., Ulrich, N., Paschke, A., Schüürmann, G., Schmitt Jansen, M., Küster, E. and Borchardt, D. (2022) 'Umsetzung des Nationalen Aktionsplans zur nachhaltigen Anwendung von Pflanzenschutzmitteln (NAP) – Pilotstudie zur Ermittlung der Belastung von Kleingewässern in der Agrarlandschaft mit Pflanzenschutzmittel-Rückständen', *Umweltbundesamt 07 / 2022*. Available at: https://www.umweltbundesamt.de/publikationen/umsetzung-des-nationalen-aktionsplans-zur-1 (Accessed: 1 April 2022).

Liška, I., Wagner, F., Sengl, M., Deutch, K., Slobodnik, J. and Paunović, M. (Eds) (2021) *Joint Danube Survey 4. Scientific Report: A Shared Analysis of the Danube River*, *ICPDR – International Commission for the Protection of the Danube River*. Available at: http://www.danubesurvey.org/jds4/publications/scientific-report.

Litchfield, H., Gupta, R., Doss, R., Bland, S. and Canerdy, T. (2015) 'Safety Evaluation of Permethrin and Indoxacarb in Dogs Topically Exposed to Activyl Tick Plus', *Journal of Veterinary Science & Technology*, 06. doi:10.4172/2157-7579.1000218.

Little, C.J. and Boxall, A.B. (2020) 'Environmental pollution from pet parasiticides.', *The Veterinary record*. England, p. 97. doi:10.1136/vr.m110.

Loeb, J. (2020a) 'Contaminated rivers are "deeply troubling"', *Veterinary Record*, 187(11), p. 425. doi:10.1136/vr.m4612.

Loeb, J. (2020b) 'What counts as responsible use of "spot ons"?', *Veterinary Record*, 187(11), p. 423. doi:10.1136/vr.m4610.

Lumaret, J.-P., Errouissi, F., Floate, K., Rombke, J. and Wardhaugh, K. (2012) 'A Review on the Toxicity and Non-Target Effects of Macrocyclic Lactones in Terrestrial and Aquatic Environments', *Current Pharmaceutical Biotechnology*, 13(6), pp. 1004–1060. doi:10.2174/138920112800399257.

Mahefarisoa, K.L., Simon Delso, N., Zaninotto, V., Colin, M.E. and Bonmatin, J.M. (2021) 'The threat of

veterinary medicinal products and biocides on pollinators: A One Health perspective', *One Health*. doi:10.1016/j.onehlt.2021.100237.

Mantingh, M. (2021) 'Monitoring bestrijdingsmiddelen en diergeneesmiddelen in haare', *Pesticide Action Network Netherlands*. Available at: https://www.pan-netherlands.org/wp-content/uploads/2021/03/pan-resultaten-haarmonsters-30-mrt-2021-fin.pdf.

McTier, T.L., Chubb, N., Curtis, M.P., Hedges, L., Inskeep, G.A., Knauer, C.S., Menon, S., Mills, B., Pullins, A., Zinser, E., Woods, D.J. and Meeus, P. (2016) 'Discovery of sarolaner: A novel, Orally administered, broad-spectrum, Isoxazoline ectoparasiticide for dogs', *Veterinary Parasitology*, 222, pp. 3–11. doi:10.1016/j.vetpar.2016.02.019.

Montforts, M., Faber, M., van Duinhoven, N., Ouwerkerk, K., Mul, M. and Veenenbos, M. (2021) 'Deltafact - Emissies van vlooienmiddelen voor huisdieren naar oppervlaktewater', *STOWA, Amersfoort, the Netherlands.* Available at: https://www.stowa.nl/deltafacts/waterkwaliteit/kennisimpuls-waterkwaliteit/emissies-van-vlooienmiddelen-voor-huisdieren (Accessed: 3 March 2022).

Mul, M., Veenenbos, M., van Vliet, J., Faber, M., van Duijnhoven, N. and Montforts, M. (2021) *Emissiereductie naar het oppervlaktewater van antivlooienmiddelen voor honden*, *CLM publication number 1078, juni 2021 (KIWIK - Kennisimpuls Waterkwaliteit rapport)*. Available at: https://kennisimpulswaterkwaliteit.nl/nl/publicaties/emissiereductie-naar-het-oppervlaktewater-van-antivlooienmiddelen-voor-honden.

Murphy, D. and Wright, I. (2020a) 'Pet parasiticides and aquatic environments', *Veterinary Record*, 187(12), p. 496. doi:10.1136/vr.m4805.

Murphy, D. and Wright, I. (2020b) 'Value of using preventive pet parasiticides', *Veterinary Record*, 186(8), p. 252. doi:10.1136/vr.m727.

Nichols, H., Gupta, R.C., Doss, R.B., Bland, S.D., Canerdy, T.D. and Zieren, J. (2014) 'Residue of Fipronil, S-Methoprene, and Amitraz in Dog Blood and in Gloves from Topical Certifect® Application: Toxicity and Safety Considerations', *J. Vet. Sc. Public Health*, 1(1), p. 003.

Oerlemans, A., Figueiredo, D.M., Mol, J.G.J., Nijssen, R., Anzion, R.B.M., van Dael, M.F.P., Duyzer, J., Roeleveld, N., Russel, F.G.M., Vermeulen, R.C.H. and Scheepers, P.T.J. (2021) 'Personal exposure assessment of pesticides in residents: The association between hand wipes and urinary biomarkers', *Environmental Research*, 199, p. 111282. doi:10.1016/j.envres.2021.111282.

Overgaauw, P.A.M., Vinke, C.M., van Hagen, M.A.E. and Lipman, L.J.A. (2020) 'A one health perspective on the human-companion animal relationship with emphasis on zoonotic aspects', *International Journal of Environmental Research and Public Health*, 17(11), pp. 1–29. doi:10.3390/ijerph17113789.

Perkins, R., Whitehead, M., Civil, W. and Goulson, D. (2021) 'Potential role of veterinary flea products in widespread pesticide contamination of English rivers', *Science of the Total Environment*, 755. doi:10.1016/j.scitotenv.2020.143560.

Perkins, R., Whitehead, M. and Goulson, D. (2021) 'Dead in the water: comment on "Development of an aquatic exposure assessment model for imidacloprid in sewage treatment plant discharges arising from use of veterinary medicinal products"', *Environmental Sciences Europe*, 33(1). doi:10.1186/s12302-021-00533-8.

Pfister, K. and Armstrong, R. (2016) 'Systemically and cutaneously distributed ectoparasiticides: A review of the efficacy against ticks and fleas on dogs', *Parasites and Vectors*. doi:10.1186/s13071-016-1719-7.

Posthuma-Doodeman, C.J.A.M. (2008) 'Environmental Risk Limits for Imidacolprid', *RIVM*. Available at: http://www.rivm.nl/bibliotheek/rapporten/601716018.pdf.

RIWA-Rijn (2021) 'Annual Report 2020 - The Rhine', *RIWA-Rijn, Vereniging van Rivierwaterbedrijven*. Available at: https://issuu.com/theredpencil/docs/annual_report_2020_-_the_red_pencil_singapore_.

Rodzaj, W., Wileńska, M., Klimowska, A., Dziewirska, E., Jurewicz, J., Walczak-Jędrzejowska, R., Słowikowska-Hilczer, J., Hanke, W. and Wielgomas, B. (2021) 'Concentrations of urinary biomarkers and predictors of exposure to pyrethroid insecticides in young, Polish, urban-dwelling men', *Science of The Total Environment*, 773, p. 145666. doi:10.1016/j.scitotenv.2021.145666.

Rust, M.K. (2020) 'Recent advancements in the control of cat fleas', *Insects*, 11(10), pp. 1–17. doi:10.3390/insects11100668.

Sadaria, A.M., Sutton, R., Moran, K.D., Teerlink, J., Brown, J.V. and Halden, R.U. (2017) 'Passage of fiproles and imidacloprid from urban pest control uses through wastewater treatment plants in northern California, USA', *Environmental Toxicology and Chemistry*, 36(6), pp. 1473–1482. doi:10.1002/etc.3673.

Sánchez-bayo, F. and Wyckhuys, K.A.G. (2019) 'Worldwide decline of the entomofauna : A review of its drivers', 232(January), pp. 8–27. doi:10.1016/j.biocon.2019.01.020.

SCHEER (2021) 'Final Opinion on Draft Environmental Quality Standards for Priority Substances under the Water Framework Directive", Imidacloprid, 7-8 October 2021', *Scientific Committee on Health, Environmental and Emerging Risks*, (October). Available at: https://ec.europa.eu/health/system/files/2021-11/scheer_o_021_0.pdf.

Selzer, P.M. and Epe, C. (2021) 'Antiparasitics in Animal Health: Quo Vadis?', *Trends in Parasitology*, 37(1), pp. 77–89. doi:10.1016/j.pt.2020.09.004.

Shotton, J. (2020) 'Time to change blanket prophylactic treatment', *Veterinary Record*, 187(12), pp. 497–498. doi:10.1136/vr.m4778.

Simon-Delso, N., Amaral-Rogers, V., Belzunces, L.P., Bonmatin, J.M., Chagnon, M., Downs, C., Furlan, L., Gibbons, D.W., Giorio, C., Girolami, V., Goulson, D., Kreutzweiser, D.P., Krupke, C.H., Liess, M., Long, E., Mcfield, M., Mineau, P., Mitchell, E.A., Morrissey, C.A., Noome, D.A., Pisa, L., Settele, J., Stark, J.D., Tapparo, A., Van Dyck, H., Van Praagh, J., Van Der Sluijs, J.P., Whitehorn, P.R. and Wiemers, M. (2015) 'Systemic insecticides (Neonicotinoids and fipronil): Trends, uses, mode of action and metabolites', *Environmental Science and Pollution Research*, 22(1). doi:10.1007/s11356-014-3470-y.

Smit, C.E., Posthuma-Doodeman, C.J.A.M., van Vlaardingen, P.L.A. and de Jong, F.M.W. (2015) 'Ecotoxicity of Imidacloprid to Aquatic Organisms: Derivation of Water Quality Standards for Peak and Long-Term Exposure', *Human and Ecological Risk Assessment: An International Journal*, 21(6), pp. 1608–1630. doi:10.1080/10807039.2014.964071.

Sok, J., Horne, P. Van and Meuwissen, M. (2020) 'The impact of the fipronil crisis on the financial performance of Dutch laying hen farms', *Parasites & Vectors*, pp. 1–7. doi:10.1186/s13071-020-04458-8.

Stanneck, D., Ebbinghaus-Kintscher, U., Schoenhense, E., Kruedewagen, E.M., Turberg, A., Leisewitz, A., Jiritschka, W. and Krieger, K.J. (2012) 'The synergistic action of imidacloprid and flumethrin and their release kinetics from collars applied for ectoparasite control in dogs and cats', *Parasites & vectors*, 5(1), pp. 73–73. doi:10.1186/1756-3305-5-73.

STOWA (2019) *Diergeneesmiddelen in het milieu huidige kennis (Rapport 2019-26)*. Available at: https://www.stowa.nl/publicaties/diergeneesmiddelen-het-milieu-een-synthese-van-de-huidige-kennis.

Tarr, A. (2020) 'Rational use of companion animal parasiticides', *Veterinary Record*, 187(2), p. 75. doi:10.1136/vr.m2908.

Teerlink, J., Hernandez, J. and Budd, R. (2017) 'Fipronil washoff to municipal wastewater from dogs treated with spot-on products', *Science of the Total Environment*, 599–600, pp. 960–966. doi:10.1016/j.scitotenv.2017.04.219.

Testa, C., Salis, S., Rubattu, N., Roncada, P., Miniero, R. and Brambilla, G. (2019) 'Occurrence of Fipronil in residential house dust in the presence and absence of pets: a hint for a comprehensive toxicological assessment', *Journal of Environmental Science and Health, Part B*, 54(6), pp. 441–

448. doi:10.1080/03601234.2019.1607133.

Toutain, C.E., Seewald, W. and Jung, M. (2017) 'The intravenous and oral pharmacokinetics of lotilaner in dogs', *Parasites and Vectors*, 10(1), pp. 1–8. doi:10.1186/s13071-017-2475-z.

Visser, A. and Van Der Wal, A.J. (2014) 'Evaluatie monitoring gewasbeschermingsmiddelen', *CLM Onderzoek en Advies*. Available at: https://edepot.wur.nl/411136.

Wagner, D.L. (2020) 'Insect declines in the anthropocene', *Annual Review of Entomology*. doi:10.1146/annurev-ento-011019-025151.

Whitehead, M. and Goulson, D. (2020) 'Martin Whitehead and Dave Goulson, coauthors of the perkins paper, respond', *Veterinary Record*, 187(12), pp. 496–497. doi:10.1136/vr.m4806.

Zhou, X., Hohman, A.E. and Hsu, W.H. (2021) 'Current review of isoxazoline ectoparasiticides used in veterinary medicine', *Journal of Veterinary Pharmacology and Therapeutics*, (December 2020), pp. 1–15. doi:10.1111/jvp.12959.

Annex I - Active substances – brief descriptions

In the following, the substances contained in ectoparasiticidal VMPs authorised for the use in cats and dogs in the EU/EEA are briefly described with information related to their use and their environmental properties. Where applicable, information is provided on measures taken for specific active substances in other EU legislative frameworks as well as on relevant conclusions that form the basis for such conclusions. The substances are arranged based on their primary mechanisms of action (primary targets). Substances for which "major use" can be anticipated as defined in **Table 4** are highlighted in bold in **Table 8** hereafter.

Table 8. Active substances authorised in ectoparasiticidal pet VMPs in the EU

Neuronal targets	Cholinergic target sites	*Organophosphates*	**Dimpylate (diazinon), phoxime, dichlorvos, tetrachlorvinphos**
		Carbamates	**Propoxur**, carbaryl
		Phosphonates	Metrifonate
		Neonicotinoids	**Imidacloprid**, dinotefuran, **nitenpyram**
		Spinosyns	Spinosad
	Voltage-gated sodium channel target sites	*Pyrethrins and pyrethroids*	1st generation: Bioallethrin, phenothrin, tetramethrin 2nd generation: **permethrin**, tetramethrin, cypermethrin, deltamethrin, **flumethrin**
		Oxadiazines	Indoxacarb
	Chloride channel target sites	*Phenylpyrazoles*	**Fipronil**, **pyripole**
		Isoxazolines and related substances	**Afoxolaner**, **esafoxolaner, fluralaner**, **lotilaner**, **sarolaner, tigolaner**
		Macrocyclic lactones	**Milbemycin**, **selamectin**, **moxidectin**, **eprinomectin**, ivermectin, doramectin
	G-protein coupled octopamine receptor	*Formamidines*	Amitraz
Growth regulator targets	Juvenile hormone mimetics		**Methoprene**, **pyriproxyfen**, fenoxycarb
	Chitin synthesis inhibitors		**Lufenuron**
Unknown target			Crotamiton

Neuronal targets as primary target sites

Most ectoparasiticide active substances act on the nervous system at the synapse or the axon. The cholinergic system is the principal target for insecticides of the organophosphate and carbamate class, which inhibit the acetylcholinesterase (AChE) to prolong the excitatory action of acetylcholine (ACh). The nicotinic ACh receptor (nAChR) is the target for neonicotinoids as competitive agonists for ACh, and for spinosad as an allosteric modulator and non-competitive antagonist. The axonal voltage-gated sodium channel is the target of pyrethrins and pyrethroids acting as modulators and indoxacarb as an inhibitor. Synaptic neurotransmission at the GABA-gated chloride channel is the primary target for the non-competitive antagonist and inhibitor fipronil as well as for the novel isoxazolines and related substances, while the GABA/glutamate-gated chloride channel is stimulated by the avermectins. The G protein-coupled octopamine receptor is the target for the agonist amitraz.

Target site resistance can be a major limiting factor for insecticide action at a common neuronal target, for instance mutations in the AChE, sodium channel and GABA-gated chloride channel for the organophosphates and carbamates, the pyrethroids and the phenylpyrazoles, respectively (R. Krieger, 2010).

Cholinergic target sites

Acetylcholinesterase targets:

Organo(thio)phosphates

Several organophosphorous compounds (QP53AF) such as dimpylate, phoxime, dichlorvos, and tetrachlorvinphos are contained in ectoparasiticidal pet VMPs authorised in the EU, with dimpylate (diazinon) being the only active substance in this chemical class with a notable use across all EU Member States.

Diazinon (dimpylate), an insecticide, acaricide and nematicide, has been banned in the EU for use in PPPs since 2007[8] and since 2010 for use in biocides[9]. The use in ectoparasiticidal VMP for animals has been suspended in many EU countries since then. No VMPs for pets or livestock containing dimpylate are currently authorised in the EU via centralised or decentralised procedures, although dozens of collars (in different sizes for cats and dogs) containing the compound are still authorised in a large number of Member States on a national basis. In some European countries dimpylate is still in use as parasiticidal VMP for sheep.

Due to its (former) use as PPP and pesticide, the environmental properties of dimpylate are well described regarding both (eco-)toxicity as well as environmental fate and behaviour. Major concerns related to the use of diazinon as PPP included risks to insectivorous birds and mammals, secondary poisoning of earthworm- and fish-eating birds and mammals due its bioaccumulation potential as well as the high toxicity for aquatic organisms and bees (EFSA, 2006b).

Carbamates

Propoxur and carbaryl (carbaril) are the only two carbamates (QP53AE) contained in ectoparasiticidal pet VMPs authorised in the EU, with propoxur being the only active substance in this chemical class

[8] 2007/393/EC: Commission Decision of 6 June 2007 concerning the non-inclusion of diazinon in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance (notified under document number C(2007) 2339). OJ L 148, 9.6.2007, p. 9–10.http://data.europa.eu/eli/dec/2007/393/oj

[9] 2010/71/: Commission Decision of 8 February 2010 concerning the non-inclusion of diazinon in Annex I, IA or IB to Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market (notified under document C(2010) 749). OJ L 36, 9.2.2010, p. 34–35.

with a notable use across all EU Member States. Pet VMPs containing propoxur as single active substance or in combination with pyrethroids are authorised in many EU Member States on a national basis, predominantly as collars against ticks and fleas.

Carbaryl was not approved as an active substance for PPPs in 2007 due to a number of concerns related to consumer health and to the environment, such as a high long-term and acute risk for insectivorous birds herbivorous mammals, respectively, as well as a high acute and long-term risk to aquatic organisms and a high risk for beneficial arthropods[10].

Propoxur is a well-known, non-systemic *N*-methylcarbamate insecticide and acaricide, which is currently not authorised as biocide or PPP in the EU. Propoxur was used in PPPs EU Member States in the past, but was never assessed and approved at EU level. In 2002 and 2009, non-inclusion-decisions for propoxur as active substance in PPPs[11] and biocides[12], respectively, was taken. Yet, its environmental and ecotoxicological properties are well described in literature, as propoxur, like many other carbamate pesticides, has long been used both for agricultural and public health purposes in non-EU countries (FAO, 2017; EFSA, 2021).

Phosphonates

Metrifonate (trichlorfon) is a decades-old organophosphorous insecticide and acaricide, which is currently only authorised in a few EU Member States in VMPs for cats and dogs in powders for topical use. It is not authorised as active substance in PPPs or biocides at EU level. Trichlorfon has been banned in the EU as active substance for the use in PPPs after the EU-wide authorisation was not granted in 2007[13] (EFSA, 2006c).

Nicotinic acetylcholine receptor targets:

Neonicotinoids

Neonicotinoids are rather new class of insecticides, which have been introduced to the market in the 1990s.

Imidacloprid is the most commonly used active substance in ectoparasiticidal pet VMPs after fipronil. It is the active ingredient in a multitude of spot-on products and collars for cats and dogs, both as single substance (QP53AX17) and in fixed combinations with pyrethroids (QP53AC54, QP53AC55). In the vast majority of Member States, these products can be purchased OTC without a veterinary prescription. In addition, imidacloprid is authorised as an endectocide spot-on solution in combination with a milbemycin (QP54AB). Dinotefuran is used in novel spot-on formulations authorised throughout Europe in combination with juvenile hormone mimetics for cats and in combination with pyrethrins for dogs. Nitenpyram is an orally administered adulticide for cats and dogs, which currently is only authorised as VMP in single EU Member States (tablets for systemic use). Nitenmpyram is neither approved as a biocide nor as a pesticide.

[10] 2007/355/EC: Commission Decision of 21 May 2007 concerning the non-inclusion of carbaryl in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance (notified under document number C(2007) 2093). OJ L 133, 25.5.2007, p. 40–41.

[11] Commission Regulation (EC) No 2076/2002 of 20 November 2002 extending the time period referred to in Article 8(2) of Council Directive 91/414/EEC and concerning the non-inclusion of certain active substances in Annex I to that Directive and the withdrawal of authorisations for plant protection products containing these substances. OJ L 319, 23.11.2002, p. 3–11.

[12] 2009/324/EC: Commission Decision of 14 April 2009 concerning the non-inclusion of certain substances in Annex I, IA or IB to Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market (notified under document number C(2009) 2566). OJ L 96, 15.4.2009, p. 37–38.

[13] 2007/356/EC: Commission Decision of 21 May 2007 concerning the non-inclusion of trichlorfon in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance (notified under document number C(2007) 2096)OJ L 133, 25.5.2007, p. 42–43.

Imidacloprid has been used for the control of sucking insects, soil insects, whiteflies, termites, turf insects or the potato beetle. In some European countries, imidacloprid is still available in pour-on products used for livestock, or—under specific preconditions—for the use in aquaculture. Initially, its toxicity to mammals, birds and fish was considered to be low. However, based on subsequent knowledge, environmental and health concerns were increasingly raised, including concerns on the negative impact on aquatic organisms, non-target arthropods, earthworms and other soil macroorganisms, so that the use of imidacloprid in PPPs is currently being phased out in Europe[14, 15]. Under the EU biocidal products regulation (Regulation (EU) No 528/2012), imidacloprid is approved as active substance for the use as insecticide and acaricide (PT18), albeit the European Chemicals Agency (ECHA) has listed imidacloprid as a candidate for substitution. More than 70 related biocidal products are currently authorised in the EEA and Switzerland, including ant bait gels and granules, fly baits, and cockroach gel baits[16]. Biocidal products containing imidacloprid are intended for professional (e.g. by pest control operators, farmers) use in bait formulations only. Comprehensive data on ecotoxicological endpoints and environmental properties are available from the authorisation process considering WWTPs as the primary receiving compartment due to the intended indoor use (ECHA, 2015).

Dinotefuran is approved as biocidal active substance[17] and the approval has been renewed in 2021[18], with two biocidal products currently being authorised in Europe[19]. The products are intended for use by professionals and for indoor use only as a spot or crevice and crack treatment at/near locations where target pests gather. Comprehensive data on ecotoxicological endpoints and environmental properties are available from the authorisation process with a special focus on indoor use, i.e. the most relevant route of environmental entry being via WWTPs (ECHA, 2014a).

Spinosyns (macrolytic lactone)

Spinosad is a selective insecticide containing structurally unique glycosylated macrolactones (spinosyns) with activity against a broad range of insect pests. Its insecticidal activity was discovered in the mid-1980s (R. Krieger, 2010). It is authorised throughout Europe as active ingredient in an ectoparasicidal VMP for systemic use in cats and dogs.

Spinosad is approved as biocidal active substance[20], with 37 biocidal products authorised in the EEA and Switzerland intended for professional use only in granules and bait stations. Comprehensive data on ecotoxicological endpoints and environmental properties are available from the authorisation process, with a special focus on the indoor use as an insecticide against adult houseflies in animal housings. Not all potential uses have been evaluated (ECHA, 2010). The renewal process as biocidal active substance is currently ongoing.

[14] Commission Implementing Regulation (EU) No 485/2013 of 24 May 2013 amending Implementing Regulation (EU) No 540/2011, as regards the conditions of approval of the active substances clothianidin, thiamethoxam and imidacloprid, and prohibiting the use and sale of seeds treated with plant protection products containing those active substances. OJ L 139, 25.5.2013, p.12-26.
[15] Commission Implementing Regulation (EU) 2018/783 of 29 May 2018 amending Implementing Regulation (EU) No 540/2011 as regards the conditions of approval of the active substance imidacloprid. OJ L 132, 30.5.2018, p. 31–34.
[16] ECHA active substance factsheet: Imidacloprid. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/37/PT18 (accessed on 15 September 2022).
[17] Commission Implementing Regulation (EU) 2015/416 of 12 March 2015 approving dinotefuran as an active substance for use in biocidal products for product-type 18. OJ L 68, 13.3.2015, p. 30–32.
[18] Commission Implementing Decision (EU) 2021/1286 of 2 August 2021 postponing the expiry date of approval of dinotefuran for use in biocidal products of product-type 18. OJ L 279, 3.8.2021, p. 39–40.
[19] ECHA active substance factsheet: Dinotefuran. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1293/PT18 (accessed on 16 September 2021).
[20] ECHA active substance factsheet: Spinosad. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/49/PT18 (accessed on 1 September 2021).

Spinosad is also approved as active substance in PPPs since 2007[21]. The renewal process, including the assessment relating to endocrine disrupting properties of the active substance is currently ongoing[22]. The environmental risks from the use as PPP and related data gaps are discussed in (EFSA, 2018c).

Axonal voltage-gated sodium channel target sites

Sodium channel modulators

Pyrethrins and pyrethroids (incl. synergists)

Pyrethrum represents an extract of the dried flowers of the daisy-like herbaceous perennial *Tanacetum cinerariaefolium*. The first commercial production of the plant began in the mid-19th century. The natural insecticidal ingredients occurring in the flowers are called pyrethrins, but their use is limited by their instability in light and air. The development of (synthetic) pyrethroids involved an iterative process of structural modifications and biological evaluation in an effort to identify compounds with increased photostability that retained the potent and rapid insecticidal activity and relatively low acute mammalian toxicity of pyrethrum. The first generation of pyrethroids, which includes bioallethrin, phenothrin (sumitrin) and tetramethrin, are still highly sensitive to light, air, and temperature and as such have been used mainly for control of indoor pests. Further developments led to the development of second-generation pyrethroids, such as permethrin, which is the first synthetic pyrethroid with sufficient photostability and substantially higher insecticidal activity as well as lower acute mammalian toxicity when compared to natural pyrethrins. Additional structural changes led to the development of deltamethrin (which is more effective than permethrin) and cypermethrin. More radical structural changes were introduced in subsequent developments, resulting in the creation of molecules such as flumethrin. Pyrethroids (including natural pyrethrins) are often mixed with the non-insecticidal synergists such as piperonyl butoxid or pyrodon (*N*-octyl bicycloheptene dicarboximide) which inhibit oxidative detoxification in insects thus enhancing the activity of the pyrethrins and pyrethroids (R. Krieger, 2010).

Many pyrethroid insecticides are used worldwide for controlling indoor and agricultural pests. Among these uses, there are a variety of pyrethrins and pyrethroids for use on animals or in their environment. They are marketed in a variety of formulations, including sprays, dusts, dips, shampoos, spot-ons, gels, foggers, ear tags and pour-ons (R. Krieger, 2010).

Pyrethrins and pyrethroids in VMPs for cats and dogs in the EU:

Several pyrethrins and pyrethroids (QP53AC) such as pyrethrum (pyrethrin), bioallethrin, phenothrin (sumitrin), **tetramethrin**, **permethrin**, **deltamethrin**, cypermethrin and **flumethrin** are contained in ectoparasiticide VMPs authorised for cats and dogs, with the four active substances highlighted above being the only compounds in this chemical class with a notable use across all EU Member States. Therefore, special focus will be given to these four substances below and in the following sections.

[21] Commission Directive 2007/6/EC of 14 February 2007 amending Council Directive 91/414/EEC to include metrafenone, *Bacillus subtilis*, spinosad and thiamethoxam as active substances. OJ L 43, 15.2.2007, p. 13–18.

[22] Commission Implementing Regulation (EU) 2021/566 of 30 March 2021 amending Implementing Regulation (EU) No 540/2011 as regards the extension of the approval periods of the active substances abamectin, *Bacillus subtilis* (Cohn 1872) strain QST 713, *Bacillus thuringiensis* subsp. Aizawai strains ABTS-1857 and GC-91, *Bacillus thuringiensis* subsp. Israeliensis (serotype H-14) strain AM65-52, *Bacillus thuringiensis* subsp. Kurstaki strains ABTS 351, PB 54, SA 11, SA12 and EG 2348, *Beauveria bassiana* strains ATCC 74040 and GHA, clodinafop, clopyralid, *Cydia pomonella Granulovirus* (CpGV), cyprodinil, dichlorprop-P, fenpyroximate, fosetyl, mepanipyrim, *Metarhizium anisopliae* (var. anisopliae) strain BIPESCO 5/F52, metconazole, metrafenone, pirimicarb, *Pseudomonas chlororaphis* strain MA342, pyrimethanil, *Pythium oligandrum* M1, rimsulfuron, spinosad, *Streptomyces* K61 (formerly '*S. griseoviridis*'), *Trichoderma asperellum* (formerly '*T. harzianum*') strains ICC012, T25 and TV1, *Trichoderma atroviride* (formerly '*T. harzianum*') strain T11, *Trichoderma gamsii* (formerly '*T. viride*') strain ICC080, *Trichoderma harzianum* strains T-22 and ITEM 908, triclopyr, trinexapac, triticonazole and ziram. OJ L 118, 7.4.2021, p. 1–5.

Pyrethrum (pyrethrin) is only included in very few topical formulations (powders, solutions, emulsions) and ear-drops, bioallethrin in a handful of shampoos, sprays and powders, phenothrin in some combination products (powders, shampoos, collars, sprays, emulsions), and cypermethrin is an ingredient of cutaneous pet VMP solutions authorised in very few Member States.

Tetramethrin is used slightly more abundantly in pet VMPs than the previously mentioned substances. As single active ingredient as well as in combination with synergists and other first generation pyrethroids it is predominantly authorised in various shampoos, powders and sprays. In some Member States, tetramethrin in combination with permethrin it is authorised in collars and in combination with cypermethrin in cutaneous solutions.

Permethrin is by far the most commonly used pyrethroid in a variety of VMP formulations for dogs, both as single active ingredient as well as in combination with other active substances. The majority of authorisations are related to spot-on formulations as single active substance or in combination with fipronil, imidacloprid or pyriproxyfen, followed by sprays, collars, shampoos and other topical formulations.

Deltamethrin is almost exclusively used as single active ingredient in collars for dogs authorised in several Member States. In the same way, flumethrin is exclusively used in collars for cats and dogs, albeit in combination with propoxur or imidacloprid.

Piperonyl butoxid is authorised as synergist in some shampoos, sprays and other topical formulations in some Member States, while pyrodon is included in the formulation of a collar.

Biocidal and pesticidal regulations:

Permethrin is approved as biocidal active substance[23] for the use as insecticide (PT18) and for the use as wood preservative (PT08, product-type 8 under (Regulation (EU) No 528/2012), with more than 35 (PT18)[24] and 140 (PT08)[25] biocidal products being authorised in Europe, respectively. Permethrin containing insecticides are intended for use by professionals (e.g. in textile fibre preservation) and non-professionals, predominantly for indoor use in a variety of formulations such as insect sprays, flea powders, foggers and smokes or ant granules and termites films. Deltamethrin is approved as biocidal active substance[26] for the use as insecticide (PT18) to control crawling and flying insects, with more than 90 authorised biocidal products containing the compound such as sprays, powders and suspensions for indoor and outdoor use by professional operators and non-professional users. Permethrin and deltamethrin are not candidates for substitution under the biocidal regulation (ECHA, 2011a, 2014b, 2014c). Flumethrin and tetramethrin are not approved as biocidal active substances, with the authorisation of tetramethrin[27] being currently under assessment.

Of the four pyrethroid substances with a notable use in pet VMPs listed above, only deltamethrin is approved as active substance for the use in PPPs since 2003[28], with the renewal procedure currently being processed[29]. Critical areas of concern from the use in PPPs include a risk to aquatic

[23] Commission Implementing Regulation (EU) No 1090/2014 of 16 October 2014 approving permethrin as an existing active substance for use in biocidal products for product-types 8 and 18. OJ L 299, 17.10.2014, p. 10–14.
[24] ECHA active substance factsheet: Permethrin (PT18). Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1342/PT18 (accessed on 27 December 2021).
[25] ECHA active substance factsheet: Permethrin (PT08). Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1342/PT08 (accessed on 27 December 2021).
[26] ECHA active substance factsheet: Deltamethrin. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/24/PT18 (accessed on 28 December 2021).
[27] ECHA active substance factsheet: Tetramethrin. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1400/PT18 (accessed on 28 December 2021).
[28] Commission Directive 2011/81/EU of 20 September 2011 amending Directive 98/8/EC of the European Parliament and of the Council to include deltamethrin as an active substance in Annex I thereto. OJ L 243, 21.9.2011, p. 16–18.
[29] Draft Renewal Assessment Report DELTAMETHRIN Vol. 1 (prepared according to the Commission Regulation (EU) N° 1107/2009). Available at: https://www.efsa.europa.eu/sites/default/files/consultation/consultation/Deltamethrin.zip (accessed on 27 December 2021).

invertebrates, bees and non-target arthropods (EFSA, 2018a). Permethrin[30] and tetramethrin[31] are not to be contained in PPPs and the authorisation of such products should be withdrawn.

Water Framework Directive:

Pyrethroids including permethrin and deltamethrin are candidate substances for inclusion in the next WL under the WFD as a group of substances to be monitored in sediment, biota and water due to the T(oxic) properties, suspected P(ersistent)B(ioaccumulative) and M(utagenic) properties as well as possible E(ndocrine)D(isruption) properties (JRC, 2020).

Oxadiazines

Indoxacarb as is a voltage-gated sodium channel inhibitor. It was authorised as active substance in ectoparasiticidal VMPs for cats and dogs throughout the EU in 2011. It is contained in a spot-on product as single active substance as well as in combination with permethrin. As active substance in biocidal products [32] it is approved since 2010, with the renewal procedure currently being in progress. Currently, four biocidal products of product-type 18 (PT18 — Insecticides, acaricides and products to control other arthropods) under the biocidal products regulation (BPR, Regulation (EU) 528/2012) such as ant gels and cockroach/fly baits are authorised in Europe[33].

In PPPs[34] it was authorised in 2006, however, the approval was not renewed in 2021[35] due to concerns related to the high long-term risk to wild mammals, in particular the long-term risk to small herbivorous mammals. Therefore, the use of PPPs containing indoxacarb will be phased out. The environmental properties and related concerns are well described in the respective assessment reports (ECHA, 2008; EFSA, 2018b).

Chloride channel target sites

GABA-gated chloride channel antagonists

Phenylpyrazoles (fiproles)

Fipronil was introduced for use as an ectoparasiticidal VMP in sprays and spot-on formulations in various European countries in the mid-1990s. Fipronil today is the most abundant active ingredient authorised in more than 550 VMPs of different strengths and topical formulations (mostly spot-on) in different EU Member States as single active substance or in combination with methoprene, permethrin or pyriproxyfen.

[30] 2000/817/EC: Commission Decision of 27 December 2000 concerning the non-inclusion of permethrin in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing this active substance (notified under document number C(2000) 4140). OJ L 332, 28.12.2000, p. 114–115.

[31] Commission Regulation (EC) No 2076/2002 of 20 November 2002 extending the time period referred to in Article 8(2) of Council Directive 91/414/EEC and concerning the non-inclusion of certain active substances in Annex I to that Directive and the withdrawal of authorisations for plant protection products containing these substances. OJ L 319, 23.11.2002, p. 3–11.

[32] Commission Implementing Decision (EU) 2021/1287 of 2 August 2021 postponing the expiry date of approval of indoxacarb for use in biocidal products of product-type 18. OJ L 279, 3.8.2021, p. 41–42.

[33] ECHA active substance factsheet: Indoxacarb (enantiomeric reaction mass S:R 75:25). Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/64/PT18 (accessed on 28 December 2021).

[34] Commission Directive 2006/10/EC of 27 January 2006 amending Council Directive 91/414/EEC to include forchlorfenuron and indoxacarb as active substances. OJ L 25, 28.1.2006, p. 24–27.

[35] Commission Implementing Regulation (EU) 2021/2081 of 26 November 2021 concerning the non-renewal of approval of the active substance indoxacarb, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending Commission Implementing Regulation (EU) No 540/2011. OJ L 426, 29.11.2021, p. 28–31.

As active substance in biocides, fipronil was approved in 2013[36], with a restriction to professional indoor use only in locations normally inaccessible after application to man and domestic animals (e.g. baits against cockroaches, ants or termites). Currently, seven biocidal products (PT18) are authorised across Europe[37].

In PPPs, fipronil was authorised at EU level in 2007[38], although the use of fipronil as PPP was strongly restricted in 2013 due to the high acute risks for bees from the use as seed treatment[39] (EFSA, 2013b). Since then, the use in agricultural applications has been phasing out.

Pyriprole is a novel phenylpyrazole, which was authorised in the EU as active substance in a spot-on formulation for dogs in 2006 in four strengths. The substance has never been approved for the use in biocides or PPPs at EU level.

Water Framework Directive:

Fipronil was proposed as candidate for the next WL under the WFD to be monitored in water due to P(ersistent), v(ery)P(ersistent) and T(oxic) properties (JRC, 2020).

GABA- and glutamate-gated chloride channel antagonist

Isoxazolines and related substances

Isoxazolines are a novel class of ectoparasiticides that has unique characteristics of rapid absorption, prolonged duration, and broad-spectrum activity against fleas/insects, ticks, and mites. The advent of isoxazolines may replace conventional treatments used so far. They were first introduced on the animal health market in 2014 introducing a potent inhibitory activity on glutamate- and GABA-gated chloride channels located in the nervous system of invertebrates as well as the possibility of oral administration in a market dominated by topical spot-ons. The oral route of administration brought benefits, particularly regarding increased customer convenience and the reduced potential for owner exposure to the compound(s). Currently, five isoxazolines (afoxolaner, esafoxolaner, fluralaner, sarolaner, lotilaner), and the closely related tigolaner are authorised in various VMPs for cats and dogs. Only one VMP containing an isoxazoline is authorised for the use in livestock (i.e. poultry). These VMPs include single-substance as well as combination products with milbemycin, selamectin, eprinomectin, emodepsid or moxidectin and pyrantel as well as topical formulations (Selzer and Epe, 2021; Zhou *et al.*, 2021).

As these substances are not authorised as biocides or PPPs, and due to regulatory framework currently in place, no studies on environmental effects or fate have been conducted in the frame of the authorisation procedures of the above-mentioned pet VMPs. In addition, specific environmental data in the public domain are scarce. Publicly available properties and ADME parameters from oral PK studies with relevance to environmental fate and effects are summarised in **Table 9**.

[36] Commission Directive 2011/79/EU of 20 September 2011 amending Directive 98/8/EC of the European Parliament and of the Council to include fipronil as an active substance in Annex I thereto. OJ L 243, 21.9.2011, p. 10–12.
[37] ECHA active substance factsheet: Fipronil. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/33/PT18 (accessed on 22 January2022).
[38] Commission Directive 2007/52/EC of 16 August 2007 amending Council Directive 91/414/EEC to include ethoprophos, pirimiphos-methyl and fipronil as active substances. OJ L 214, 17.8.2007, p. 3–8.
[39] Commission Implementing Regulation (EU) No 781/2013 of 14 August 2013 amending Implementing Regulation (EU) No 540/2011, as regards the conditions of approval of the active substance fipronil, and prohibiting the use and sale of seeds treated with plant protection products containing this active substance. OJ L 219, 15.8.2013, p. 22–25.

Table 9. Partitioning coefficients (*n*-octanol/water) and selected ADME parameters from PK studies of isoxazolines in dogs following oral administration.

Active substance	Partitioning coefficient log K_{ow} measured/ (*predicted*[40])	Plasma protein binding	Plasma half-life $T_{1/2}$ (oral)	Elimination	Major excretion pathway	References
Afoxolaner	-/(6.7)	> 99,9%	15 days	Parent + metabolite (hydroxylate)	Biliary/ faeces + urinary	(Letendre *et al.*, 2014; EMA/CVMP, 2020a)
Fluralaner	5.35/(5.6)	~ 100%	12–15 days	Majority unchanged	Biliary/ faeces	(Kilp *et al.*, 2014; EMA/CVMP, 2021a)
Sarolaner	-/(3.4)	> 99,9%	11–12 days	Majority unchanged	Biliary/ faeces	(McTier *et al.*, 2016; EMA/CVMP, 2020b)
Lotilaner	5.3/(6.6)	High	30 days	Majority unchanged	Biliary/ faeces	(Toutain *et al.*, 2017; EMA/CVMP, 2021b)

For fluralaner, Lahr et al. (2019) defined a hazard limit of 0.47 ng/L for surface waters based on a chronic NOEC of 47 ng/L in *Daphnia magna* (EMA/CVMP, 2022). In a PBT assessment, fluralaner has been classified as persistent/very persistent (P/vP) in soil and aerobic freshwater sediment, while it is clearly not persistent in freshwater and anaerobic freshwater sediment (EMA/CVMP, 2022).

Glutamate-gated chloride channel activator

Macrocyclic lactones

Macrocyclic lactones (avermectins and milbemycins) are closely related 16-member macrocyclic lactones produced through fermentation by soil-dwelling *Streptomyces* and commercially are only used in veterinary medicine. The use of macrocyclic lactones in livestock is of concern from an ecotoxicological standpoint. The persistent presence of these substances in the faeces of treated cattle produces an adverse effect against invertebrates that are important for dung degradation and nutrient recycling in soil (R. Krieger, 2010).

At European level, milbemycin oxime and selamectin are only authorised in VMPs for the use in companion animals. While for these two substances only few ecotoxicological data are available (Lumaret *et al.*, 2012), the knowledge for the other macrocyclic lactones authorised in pet VPMs is fairly abundant.

A variety of VMPs for the use in mammalian food-producing species authorised in the EU/EEA contain ivermectin, doramectin, eprinomectin and moxidectin**,** and many of them already were subject in referral procedures for environmental safety reasons such as (potential) PBT properties, risks to dung

[40] National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 25154249, Afoxolaner. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Afoxolaner (accessed on 27 December 2021).
National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 25144319, Fluralaner. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Fluralaner (accessed on 27 December 2021).
National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 73169092, Sarolaner. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Sarolaner (accessed on 27 December 2021).
National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 76959255, Lotilaner. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Lotilaner (accessed on 27 December 2021).

fauna and/or the aquatic environment as well as the need for the implementation of adequate RMMs (Fabrega and Carapeto, 2020). An eprinomectin-containing VMP for cattle with a slow-release formulation was refused marketing authorisation in the EU based on its environmental safety profile (i.e. serious long-term risk to dung fauna; (EMA/CVMP, 2019).

G protein-coupled octopamine receptor agonist

Formamidines

Amitraz is an acaricide with a complex pharmacological activity (R. Krieger, 2010). In the past, it was used on top fruit, cotton and hops and as VMP for the treatment of ectoparasites in pigs, cattle, sheep and goats applied topically as spray or as a dip (EMA/CVMP, 1998). Today, in the EU/EEA, it is only used in ectoparasiticidal VMPs presented as topical formulations and collars for dogs and on stripes for bee hives. Amitraz was banned for use in PPPs in 2004[41] and has never been authorised as biocide in the EU.

Growth regulator targets

Every organism follows a programmed course of growth and development carefully synchronized for species propagation and environmental integration. Compounds that disrupt these delicate hormone-guided processes serve as insect growth regulators (IGRs). Insect development is controlled by a balance in time and amount of juvenile hormone to stay young, and growth and differentiation hormone or ecdysone to develop, molt, and become an adult. Juvenile hormone mimetics and analogues such as methoprene are very effective and selective, but provide slow control. The actual mode of action of chitin biosynthesis inhibitors such as that of the benzoylphenyl urea insecticide lufenuron remains unclear (R. Krieger, 2010).

Juvenile hormone mimetics

Pyriproxyfen is on the market in dozens of ectoparasiticidal VMPs in combination with permethrin in cutaneous sprays and solutions and shampoos for dogs since the late 1990s. Since the early 2000s, dozens of spot-on products as single-substance formulations and in combination with other active substances, mostly phenylpyrazoles, followed. Pyriproxyfen was authorised as biocidal substance in 2015[42] and is intended for professional use for the control of flies in farm applications (such as cattle pens, pig and poultry houses, indoor manure heaps and in rotting silage), WWTPs and for controlling mosquitoes in both running and standing water (ECHA, 2012). Currently, 8 related biocidal products, including combination products for indoor use such as flea sprays for the pet's environment, sprays against lice or gels against cockroaches and ants are authorised at EU level[43]. In 2020, pyriproxyfen was approved as active substance for use in PPPs[44] as an insecticide, albeit environmental concerns were identified (EFSA, 2019).

Methoprene (*S*-methoprene) is on the market across Europe in veterinary spot-on solutions for cats and dogs in combination with fipronil since the early 2000s. In 2020, an additional spot-on formulation

[41] 2004/141/EC: Commission Decision of 12 February 2004 concerning the non-inclusion of amitraz in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing this active substance (notified under document number C(2004) 332). OJ L 46, 17.2.2004, p. 35–37.

[42] Commission Directive 2013/5/EU of 14 February 2013 amending Directive 98/8/EC of the European Parliament and of the Council to include pyriproxyfen as an active substance in Annex I thereto. OJ L 44, 15.2.2013, p. 14–17.

[43] ECHA active substance factsheet: Pyriproxyfen. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/61/PT18 (accessed on 24 January 2022).

[44] Commission Implementing Regulation (EU) 2020/968 of 3 July 2020 renewing the approval of the active substance pyriproxyfen in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. OJ L 213, 6.7.2020, p. 7–11.

in combination with 3 other active substances was authorised throughout the EU/EEA for use in cats. *S*-Methoprene was approved as biocidal substance in 2015[45] and, as such, is intended for indoor use in bait stations by professional and non-professional users for the control of Pharaoh's ants (*Monomorium pharaonis*) (ECHA, 2016). Currently, more than 45 biocidal products such as ant gels and larvicides against mosquitoes are authorised in the EU[46]. Methoprene is not approved for use in PPPs.

Fenoxycarb is the active ingredient in a cutaneous spray for dogs in combination with permethrin in at least one EU member State. Fenoxycarb was authorised as biocidal active substance in wood preservatives in 2013, although no biocidal products are currently authorised at EU level[47]. It has been authorised as active substance in PPPs in 2011[48] for the use as insecticide on apples and pears, albeit environmental concerns were identified (EFSA, 2010).

Chitin synthesis inhibitors

Since the mid-1990s, lufenuron has been on the market as ingredient in oral suspensions, injections and tablets for cats and dogs. Since then, many products are still authorised throughout Europe via national authorisations.

In PPPs it has been authorised in 2009[49]. However, as lufenuron meets the criteria for being considered a persistent and bioaccumulative substance, it was included in the list of candidates for substitution in 2015[50]. The approval for the use as active substance for use in PPPs expired in 2019[51]. Lufenuron has never been approved for the use as active substance in biocides.

Unknown targets

The mechanism(s) of action of crotamiton is (are) unknown. The only use is in topical formulations for the treatment against mites in human and veterinary medicinal products.

[45] Commission Implementing Regulation (EU) No 91/2014 of 31 January 2014 approving *S*-methoprene as an existing active substance for use in biocidal products for product-type 18. OJ L 32, 1.2.2014, p. 13–15.
[46] ECHA active substance factsheet: *S*-Methoprene. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1386/PT18 (accessed on 24 January 2022).
[47] ECHA active substance factsheet: Fenoxycarb. Available at: https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/31/PT08 (accessed on 24 January 2022).
[48] Commission Directive 2011/20/EU of 2 March 2011 amending Council Directive 91/414/EEC to include fenoxycarb as active substance and amending Decision 2008/934/EC. OJ L 58, 3.3.2011, p. 45–48.
[49] Commission Directive 2009/77/EC of 1 July 2009 amending Council Directive 91/414/EEC to include chlorsulfuron, cyromazine, dimethachlor, etofenprox, lufenuron, penconazole, tri-allate and triflusulfuron as active substances. OJ L 172, 2.7.2009, p. 23–33.
[50] Commission Implementing Regulation (EU) 2015/408 of 11 March 2015 on implementing Article 80(7) of Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and establishing a list of candidates for substitution. OJ L 67, 12.3.2015, p. 18–22.
[51] Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 1–186.