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Committee for Veterinary Medicinal Products (CVMP)

Concept paper for the development of a guideline on the methodology of environmental risk assessment for ectoparasiticidal VMPs for cats and dogs

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1. Introduction

In the European Union, the environmental risk assessment (ERA) for veterinary medicinal products (VMPs) is conducted in two phases (Phase I and Phase II), in line with VICH guidelines (GL) 6 [1] and 38 [2]. VMPs for which the ERA is concluded in Phase I are those for which the environmental emissions resulting from their use are considered to be negligible and, therefore, their exposure level in the environment is not expected to cause a risk to non-target organisms. A Phase I ERA does not require information on fate, behaviour and effects data of the active substance contained in the VMP in question.

The environmental exposure resulting from the use of VMPs in companion animals has been considered negligible based on the assumption that non-food-producing animals are not intensively reared and that therefore the administration of VMPs to these animals can be considered as an 'individual treatment' (see question 3 in VICH GL6 for details).

Based on the data currently available, which was assessed by CVMP in a dedicated reflection paper [3], it appears that the validity of this assumption (i.e. that the environmental exposure from the use of VMPs in companion animals can be considered as negligible) is open to question. While the existence of data gaps is acknowledged, the CVMP considers that the available information sufficiently demonstrates that, for certain ectoparasiticidal VMPs to be identified (see section 4 below for details), the current approach to stop the ERA in Phase I should be revisited.

This concept paper has been prepared with the aim to develop guidance on the assessment methodology to be used where the current default assumption is not considered to be appropriate for ectoparasiticidal VMPs, as well as guidance on the nature of data to be provided in such cases [3].

2. Problem statement

There is growing concern that residues of active substances used in ectoparasiticidal VMPs for non-food-producing animals in surface waters may exceed predicted no effect levels (PNECs) in both wastewater effluent and downstream of wastewater treatment facilities, which suggests that such VMPs may contribute to a large-scale contamination of freshwaters [4–7]. The presence of such residues in the terrestrial compartment via direct and/or indirect emissions from VMP use cannot be disregarded, as evidence of exposure in the terrestrial compartment is also becoming increasingly available, albeit (still) to a lesser extent [8, 9].

However, there is currently no guidance available on how an ERA for VMPs for companion animals should be undertaken in those cases where one is considered necessary.

3. Discussion (on the problem statement)

As detailed in the above-mentioned reflection paper [3], a full and harmonised product-based ERA approach for specific environmental compartments or target species is not yet available, because (i) input data, models and strategies for assessing environmental exposure still need to be elaborated; and (ii) there are data gaps on environmental fate and effects data, especially for novel substance classes. Suitable exposure scenarios would need to be developed to perform a Phase II ERA. More recently, further studies, e.g. on down-the-drain pathways [4], have been published, in which a quantitative assessment of the aquatic pollution by imidacloprid and fipronil applied as spot-on parasiticides to dogs was further evaluated.

3.1. Exposure

Diepens et al. [8] have recently conceptualised the transfer of veterinary flea products from pet dogs to the environment (**Figure 1**). This scheme covers all potential routes of exposure of a VMP used in non-food-producing animals to the environment and opens the path to developing models for environmental contamination and impact assessment.

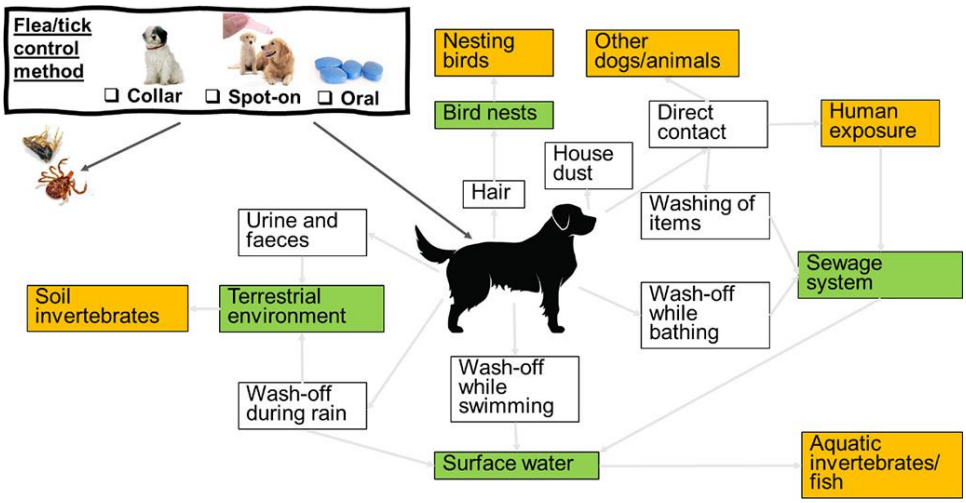

Figure 1: Environmental contamination and impact of parasiticides used in pets (figure taken from Diepens et al. [2023; DOI: https://doi.org/10.1016/j.scitotenv.2022.159550], published under the terms of the CC BY-NC-ND 4.0 license [https://creativecommons.org/licenses/by-nc-nd/4.0/])

This study, and others available, along with existing guidance on the ERA for human and veterinary medicinal products [10, 11], will serve as a valuable basis for the development of relevant exposure models. Regarding down-the-drain pathways of ectoparasiticidal VMPs used in cats and dogs, elements of methodologies from the 'predicted environmental concentration' (PEC) estimation for human medicines and other frameworks may be relevant.

The exposure models to be developed will need to consider:

- The route/method of administration (collar, spot-on, oral, other methods such as injection), and management of the treated animal and its environment (e.g. washing of the animal and fabrics in close contact, grooming, bathing);
- The mode of action of the active substance(s) (topically acting, systemically acting), together with the pharmacokinetic properties (distribution and elimination from the coat, excretion patterns) of the active substance(s) considering the posology and frequency of use;
- Available measured data (for model validation).

Different exposure models may have to be developed depending on these parameters, whereby, as is usual with such methods, adequate simplifications of the exposure pathways may have to be made.

Release into surface waters including sediments

The main exposure scenario to be modelled, in line with the conclusions of the EMA reflection paper [3] and recent publications on down-the-drain pathways of residues from the use of pet VMPs, should be the release into surface waters including sediments (i.e. derivation of a PEC for surface water [PEC_{sw}], and sediment [PEC_{sed}]). These should include the following routes of exposure:

Direct exposure routes: swimming, bathing, excretion via faeces and urine

- Direct exposure routes: swimming, bathing, excretion via faeces and urine;
- Indirect exposure routes via wastewater (wash-off from items and the animal [e.g. during/after bathing and/or washing of blankets]).

Other receiving compartments

Methodologies to investigate further exposure scenarios should be developed, if considered relevant. These may include, for example, the release into soil or the exposure of the groundwater compartment.

In soil, at least 3 different routes of entry into the environment should be considered:

- Indirect exposure from sewage sludge considers wash-off from bathed animals as well as washing of blankets, house cleaning, etc.;
- Direct exposure from grooming/washing outdoors;
- Direct exposure from faeces and urine in the environment.

If considered relevant, soil contamination needs to be assessed via appropriate scenarios to estimate PECs. This, for example, may occur via direct exposure of faecal and or urinary excretions. There is evidence that insects (such as house flies) feed on faeces of dogs [12] and the potential impact of the presence of ectoparasiticidal active substances excreted in faeces could have a toxicological impact on dung fauna, and other terrestrial species, thereby advocating for an appropriate scenario.

Groundwater exposure is a result of bank filtration or pore water contamination. Similar scenarios may need to be adapted or developed to estimate wastewater contamination with residues of pets' parasiticides after bathing or washing of pets and related material, as suggested by Perkins et al. [4, 5].

3.2. Fate and effects

Consideration is needed as to which specific fate and effects data should be necessary for a targeted assessment for ectoparasiticidal VMPs for cats and dogs. The data requirements for food-producing species in VICH GL38 [2] will serve as a base to identify the fate and effects studies that would allow to conduct the risk assessment and to develop appropriate risk mitigation measures. However, other potential fate and effects specific for companion animals may be considered when elaborating the risk assessment.

4. Recommendation

The objective is to develop a guideline on the methodology for a tailored Phase II ERA to evaluate the exposure, fate and effects that the use of ectoparasiticidal VMPs for cats and dogs may have on the environment. Further, the aim is to define data requirements for the preparation of such an ERA by the

applicants for submission in the frame of a marketing authorisation application. The scope of the methodology will be limited to ectoparasiticidal VMPs for cats and dogs only.

It is intended to obtain the views of all interested parties through the public consultation of this concept paper.

Following this consultation, it is the intention of the CVMP to hold a workshop in order to exchange views with researchers, industry and competent authorities in this area.

The developed methodology shall be in line with the requirements for an environmental risk assessment as laid out in Regulation (EU) 2019/6[1], and will follow the same principles as defined for the environmental impact assessment for VMPs used in food-producing animals (i.e. VICH GL38 [2] and in the 'Guideline on the environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38' [EMA/CVMP/ERA/418282/2005] [11]).

Therefore, the interpretation of available real world monitoring data and measured environmental concentrations regarding a substance's source (i.e. VMP or non-VMP use) or providing evidence of environmental effects that can be directly linked to the use of such VMPs is not within scope of this development process. These aspects have been covered in the relevant reflection paper [3] and in more recent publications [4, 6, 7].

The proposed guideline is planned to cover the following aspects:

- The target species, types of VMPs/active substances and pattern of use in scope of a tailored Phase II ERA for non-food producing animals;
- The routes/methods of administration of the VMP, its mode(s) of action and the resulting environmental exposure scenarios;
- The routes of entry into the environment, with a focus on down-the-drain pathways and direct soil and water contamination. Exposure modelling for the relevant routes;
- The environmental fate and effects data to be provided, including published data and scientific publications, that will allow for an ERA;
- Discussion of appropriate risk mitigation measures.

5. Proposed timetable

- Adoption of the concept paper by CVMP for release for consultation: Q2/2025.
- Release for 3-month public consultation: Q2/2025.
- Start of the elaboration of the draft guideline: Q4/2025–Q1/2026.
- Adoption by CVMP for release for consultation: Q4/2027.
- End of consultation: Q1/2028.
- Discussion of comments received and revision of guideline, including the potential organisation of a workshop: Q1/2028–Q2/2028.
- Adoption of revised guideline by CVMP: Q4/2028–Q1/2029.

[1] Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, OJ L 4, 7.1.2019, p. 43–167. Available at: http://data.europa.eu/eli/reg/2019/6/oj (accessed on 5 March 2025).

6. Resource requirements for preparation

The guideline will be prepared using adequate time for discussions during ERAWP plenary meetings as well as ad-hoc virtual meetings, as required. A rapporteur and a co-rapporteur from the ERAWP might be nominated. The development of the guideline will very likely require the organisation of a workshop with specialists from third parties. The EMA secretariat will coordinate the consultation and communication between third parties as well as the public consultation. Adequate time at plenary CVMP meetings will be required to discuss and adopt the various drafts of the guideline.

7. Impact assessment (anticipated)

The anticipated guideline will enable applicants to design, carry out and report on the environmental exposure, fate and effects of parasiticidal VMPs for companion animals based on agreed criteria, whenever an ERA could be required in the frame of a relevant regulatory procedure. This will provide applicants with a better predictability of requirements and acceptability of their marketing authorisation applications for parasiticidal VMPs for companion animals and will enhance harmonisation of the design and interpretation/assessment of such studies by applicants and regulators.

8. Interested parties

Industry, commercial consultancies, research organisations and academia, regulators and veterinarians.

9. References

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