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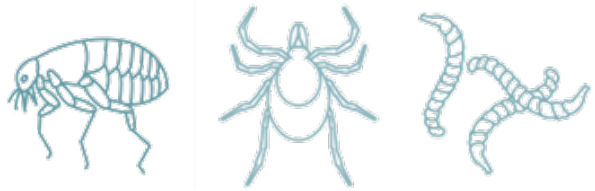
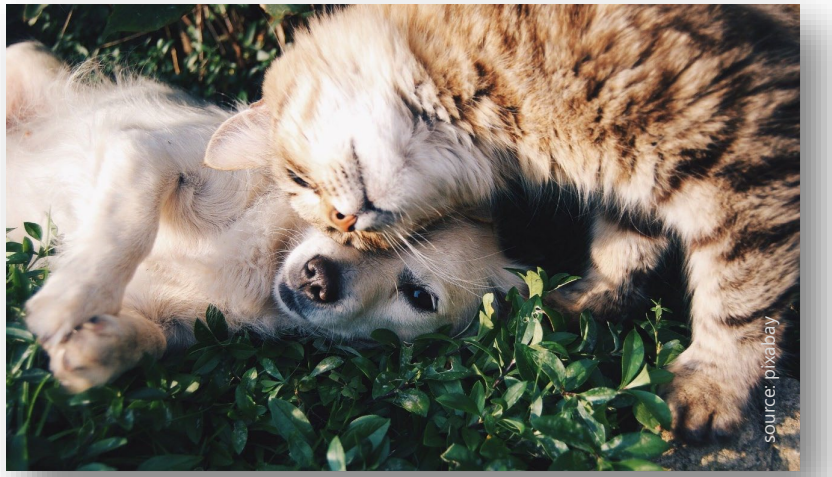
Environmental Safety of Parasiticidal Veterinary Medicinal Products (VMPs) for Cats and Dogs in the EU/EEA

EMA Veterinary Awareness Day | 12-13 September 2023
European Medicines Agency, Amsterdam





Haru Kroneis

Austrian Medicines and Medical Devices Agency (AGES-MEA/BASG), Vienna, Austria

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  H. Kroneis

Overview

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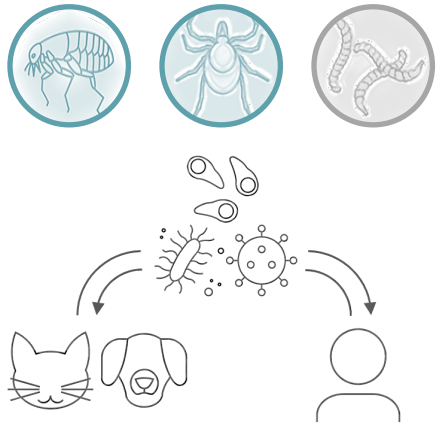
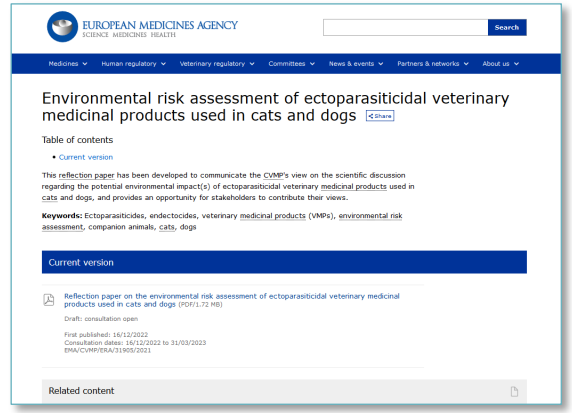
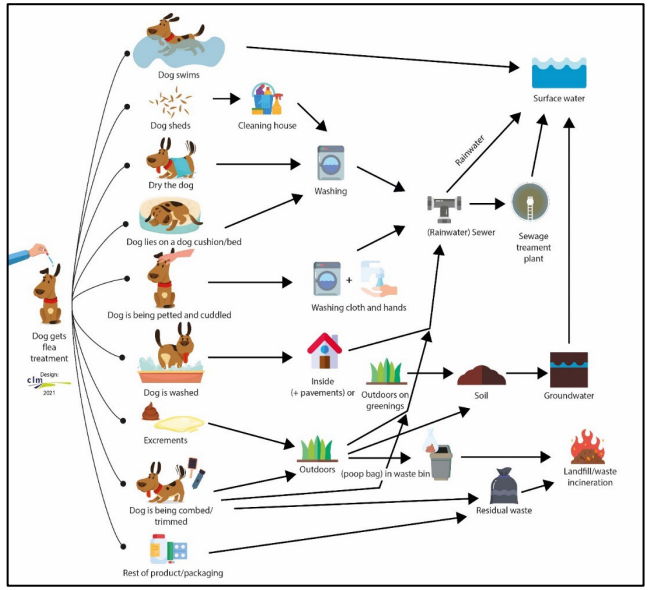
- Background (parasites and One Health)
- General information on the EMA/CVMP Reflection Paper
- Types of ectoparasiticidal VMPs and active substances authorised
- Environmental exposure pathways and monitoring data
- Addressing knowledge gaps …
- Take home messages








source: AGES Picturepark

Background (1/2)

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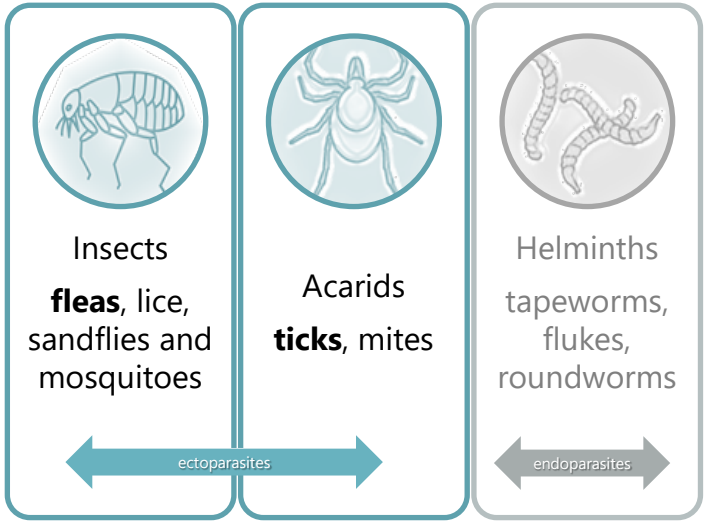
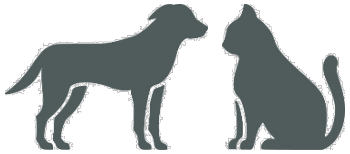
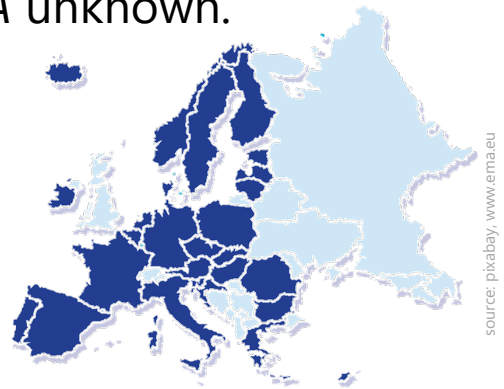
Parasites, cat and dog population and public health



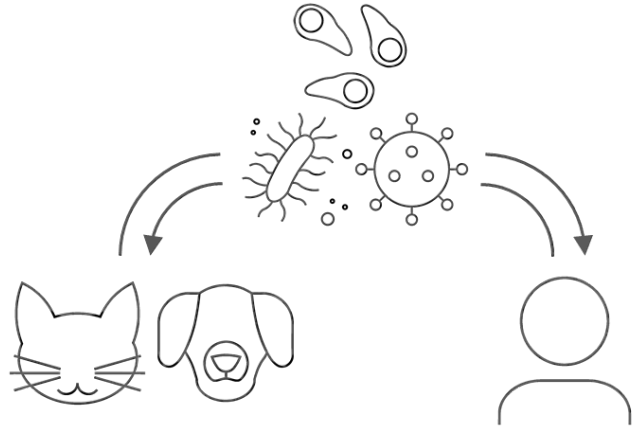
- Ectoparasites (and endoparasites)
  - Important vectors of pathogens (bacterial, viral, helminth or protozoan).
  - Some pose a serious threat to animal + public health (zoonoses).
  - Infested animals act as source of infestation to animals and humans.



- Population of cats and dogs
  - ~ 138 million *pet animals* in EU/EEA numbers increasing[#]
  - Number of *stray/abandoned animals in EU/EEA* unknown. (estimate for Europe ~ 100 million[§])
  - The extent and frequency of treatment with parasiticidal VMPs is unknown.



source: pixabay, www.ema.eu



[#] According to data published European Pet Food Industry association (FEDIAF 2020)
[§] including non-EU/EEA countires; Overgaauw et al. 2020

Background (2/2)

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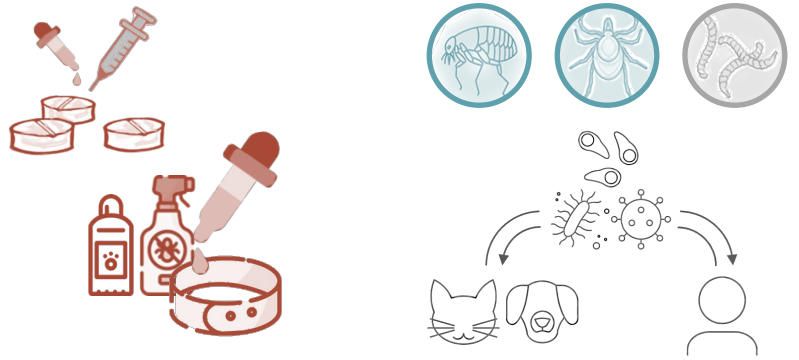
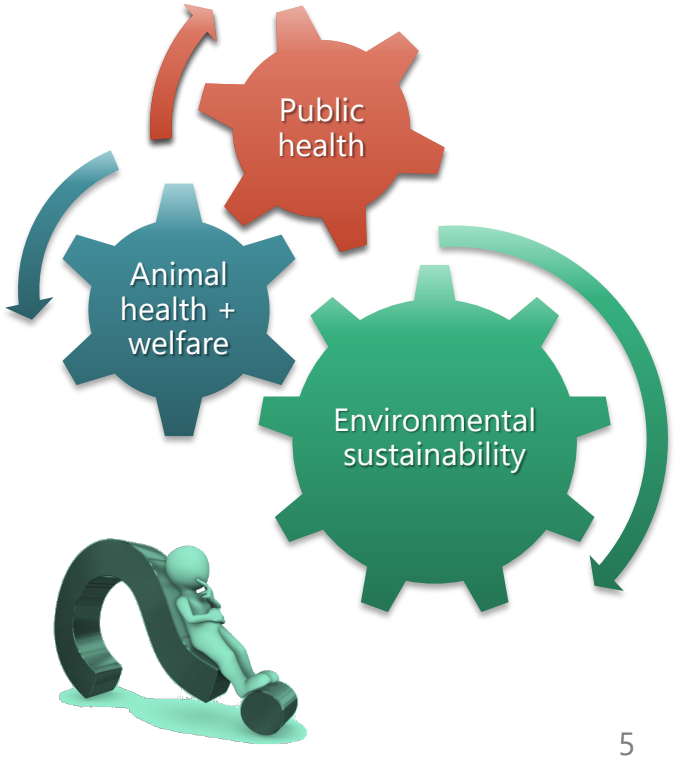
Parasites, treatment and prevention, "One Health",

- A multitude of parasiticidal veterinary medicinal products (VMPs) on the market, however…
  - such VMPs should be seen as **part** of a treatment and prevention plan of parasitic infestations,
  - which should consider multiple factors
  - e.g. clinical diagnosis, lifestyle, age, health of animal, travel plans, owner compliance, non-medical measures etc.)





„One Health"

- Public health (zoonoses; household and community level)
- Animal welfare (nuisance from ticks and fleas) and
- Animal health (cutaneous lesions, allergies, vector-borne diseases)
- Environmental sustainability is currently not considered.

The EMA/CVMP Reflection Paper (1/3)

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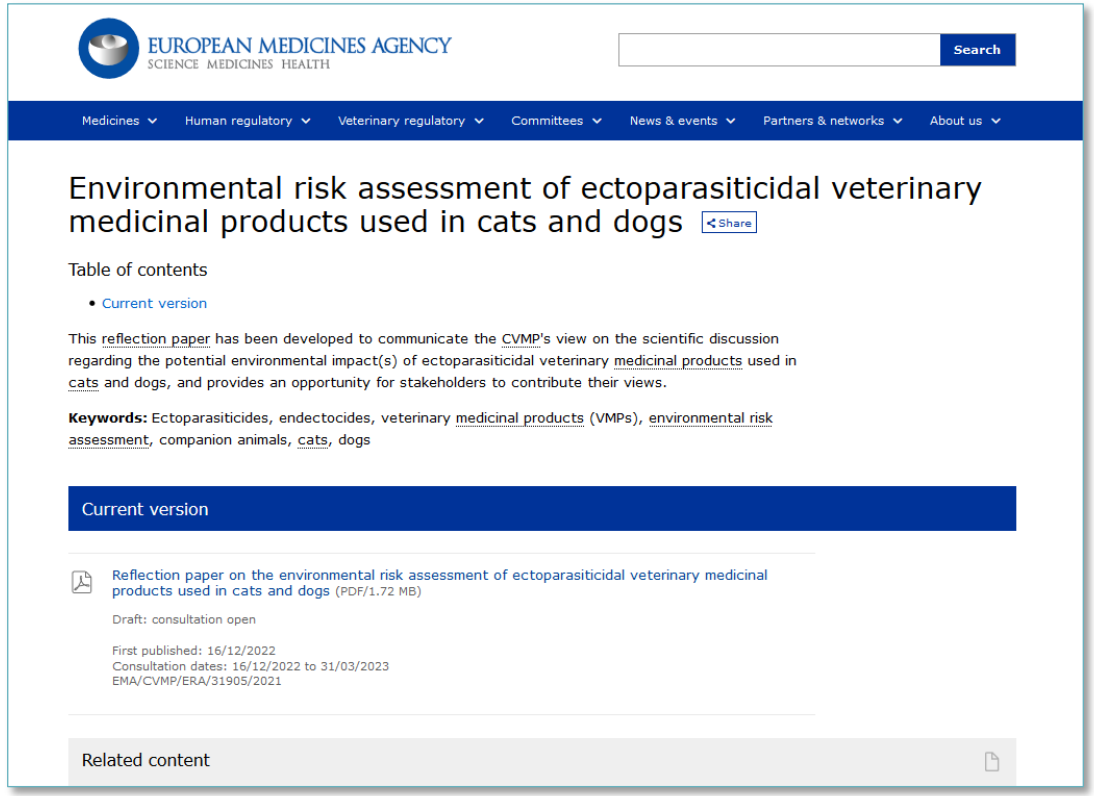
Problem statement in a nutshell …

- Ectoparasiticidal VMPs have an *insecticidal* and *acaricidal* activity that *could impact free-living non-target* insects, mites and other *arthropod species* and thus impact ecosystems.
- Current *international legislation* (VICH GL 6) considers these *risks for the environment* from the use of such VMPs on cats and dogs (as non-food producing animals) to be *negligible* due to the small quantities used on each individual animal.
- This assumption may not be appropriate anymore.
- Reflection paper has been developed to communicate the CVMP's view on the current state of the scientific discussion.



EMA *(European Medicines Agency);* **CVMP** *(Committee for Veterinary Medicinal Products);* **VICH** *(International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products);* **VMP** *(Veterinary Medicinal Product)*

The EMA/CVMP Reflection Paper (2/3)

Why was the elaboration of the reflection paper initiated?

- **Several publications attributed**, at least to some extent, the **presence of 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 products for pets** (e.g. Sadaria *et al.*, 2017; Teerlink *et al.*, 2017). More followed.

- A potential link between the death of songbird chicks and the treatment of dogs with parasiticidal VMPs (fipronil and imidacloprid) was highlighted by Guldemond *et al.* (2019)

⇨ **Potential** (environmental) **adverse event** following VMP use

- Concept paper
  (explaining purpose, aims and scope)
  - **Public consultation**: 23/04/2020 - 31/10/2020

- Reflection paper
  (communicating current state of scientific discussion)
  - **Public consultation**: 16/12/2022 – 31/03/2023

The EMA/CVMP Reflection Paper (3/3)

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Aims and Scope – a pragmatic approach to achieve objectives

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

To achieve objectives scope narrowed down to

- **Cats and dogs, veterinary medicines** (VMPs), **ecto**parasiticides (incl. end*ecto*cides), **outdoor environment**, VMPs authorised in **EU/EEA**

Product types and active substances authorised

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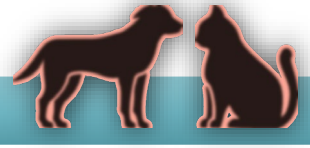
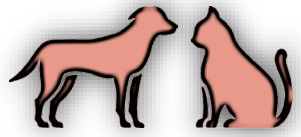
.... as per product type (method of administration) and mode of action

- About **40 substances** active against external (*ectoparasiticides*) or against internal + external parasites (*endectocides*) are included in ectoparasiticidal VMPs for cats and dogs in the EU/EEA.
- Many also used as biocide and/or pesticide ("multi-use" substances).



"locally acting"



"systemically acting"

Spot-ons

- „Major use" in spot-ons: **fipronil, permethrin, imidacloprid; + methoprene, pyriproxyfen**
- Also in use: pyriprole, dinotefuran, indoxacarb

Collars

- „Major use" in collars: **dimpylate, permethrin, flumethrin, + propoxur, imidacloprid**
- Also in use: amitraz, tetrachlorvinphos,deltamethrin, fipronil, tetramethrin

Sprays, shampoos, powders

- „Major use" in sprays, shampoos, powders: **various pyrethroids, fipronil, + piperonyl butoxide**
- Also in use: propoxur, carbaryl, formamidine, dichlorvos, dimpylate, metrifonate, phoxime

Tablets, spot-ons, injections

- „Major use" as tablets, spot-ons and injections: **Lufenuron; Afoxolaner, esafoxolaner, fluralaner, sarolaner, lotilaner** and **tigolaner**
- Some endectocidal macrocyclic lactones

Environmental exposure considerations

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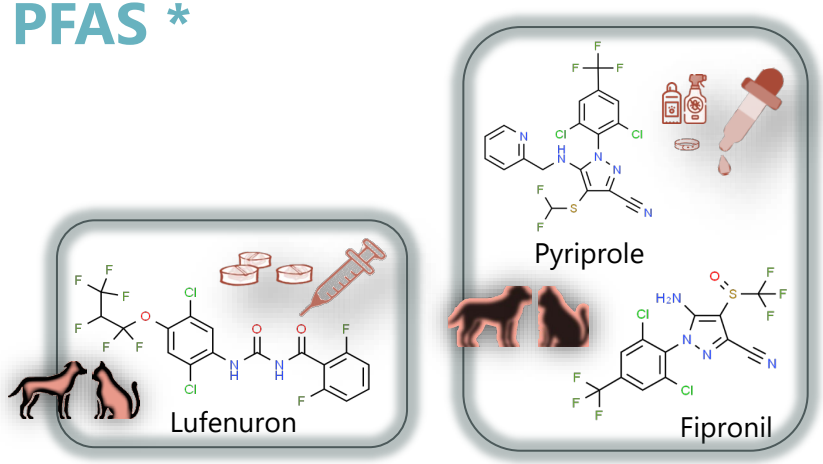
Some active substances in these VMPs are classified as PFAS *

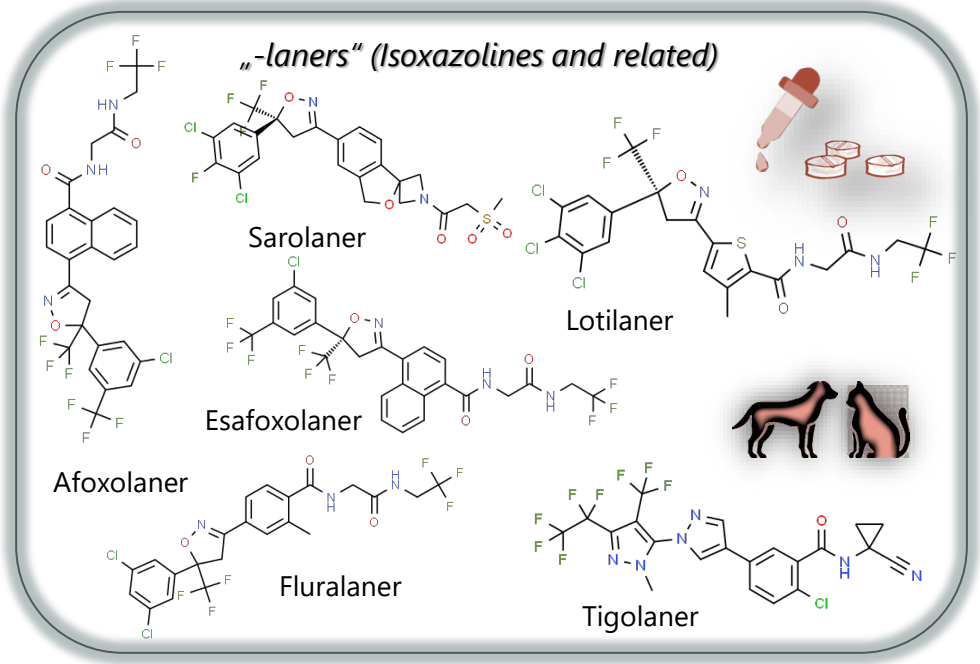
* Non-polymeric PFASs according to OECD definition

- PFAS either are, or degrade to, persistent chemicals that accumulate in humans, animals and the environment.

  ⇨ Relevant for **environmental exposure** considerations

Emerging chemical risks in Europe — 'PFAS' — European Environment Agency (europa.eu)





All structures retrieved via www.chemspider.com

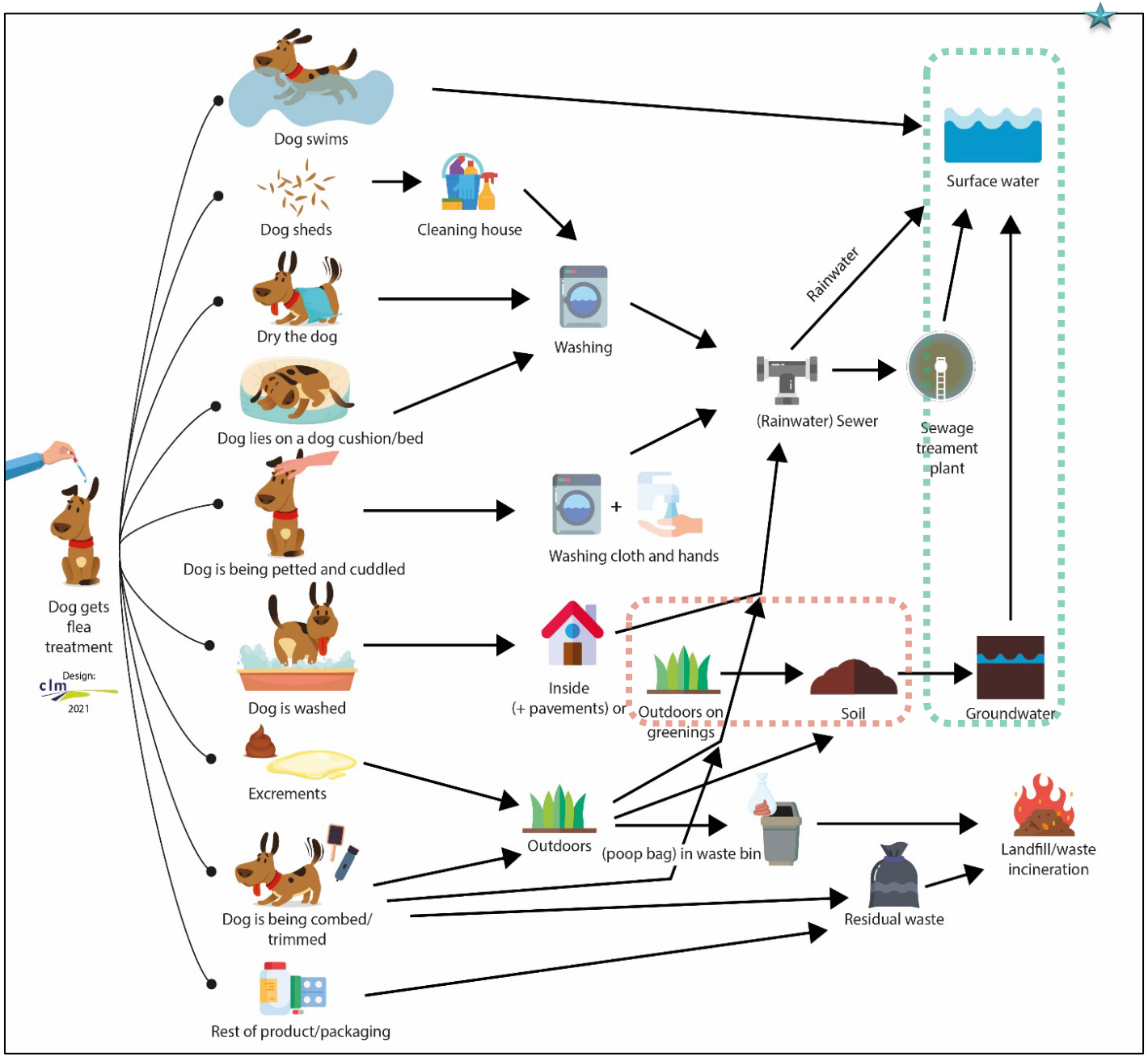
Environmental exposure pathways

Conclusions in RP

- **Surface waters (including sediments)** possibly **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 not yet quantified (e. g. in peri-urban ecosystems).

⇨ *environmental exposure pathways for cats and dogs are **different to** those described in **exposure models for food-producing animals***



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

Monitoring data for the aquatic compartment

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Conclusion: A contribution of pet VMPs cannot be ruled out

- Case study 1: Presence of imidacloprid, fipronil and dimpylate in the **Danube river basin**: findings of the fourth Joint Danube Survey (4JDS)
- Case study 2: Imidacloprid in **Spanish WWTPs** (Waste Water Treatment Plants)
- Case study 3: Fipronil and imidacloprid in **English WWTPs and rivers**
- Case study 4: Imidacloprid and fipronil in **Dutch WWTPs and surface water**
- Case study 5: **French** watch list monitoring campaigns: imidacloprid
- Case study 6: **German small water monitoring** pilot study
- Case study 7: Imidacloprid and fipronil in the **San Francisco Bay** area (CA, USA)

It cannot be ruled out that veterinary medicines (VMPs) used in pets

- contribute to fipronil and imidacloprid concentrations measured in urban wastewater effluents and [...]
- contribute to substance concentrations that pose a risk to the aquatic environment in the vicinity of WWTP discharges.
- Presence of substances in sewage sludge is mostly not known

WWTP ..... *Waste Water Treatment Plant*

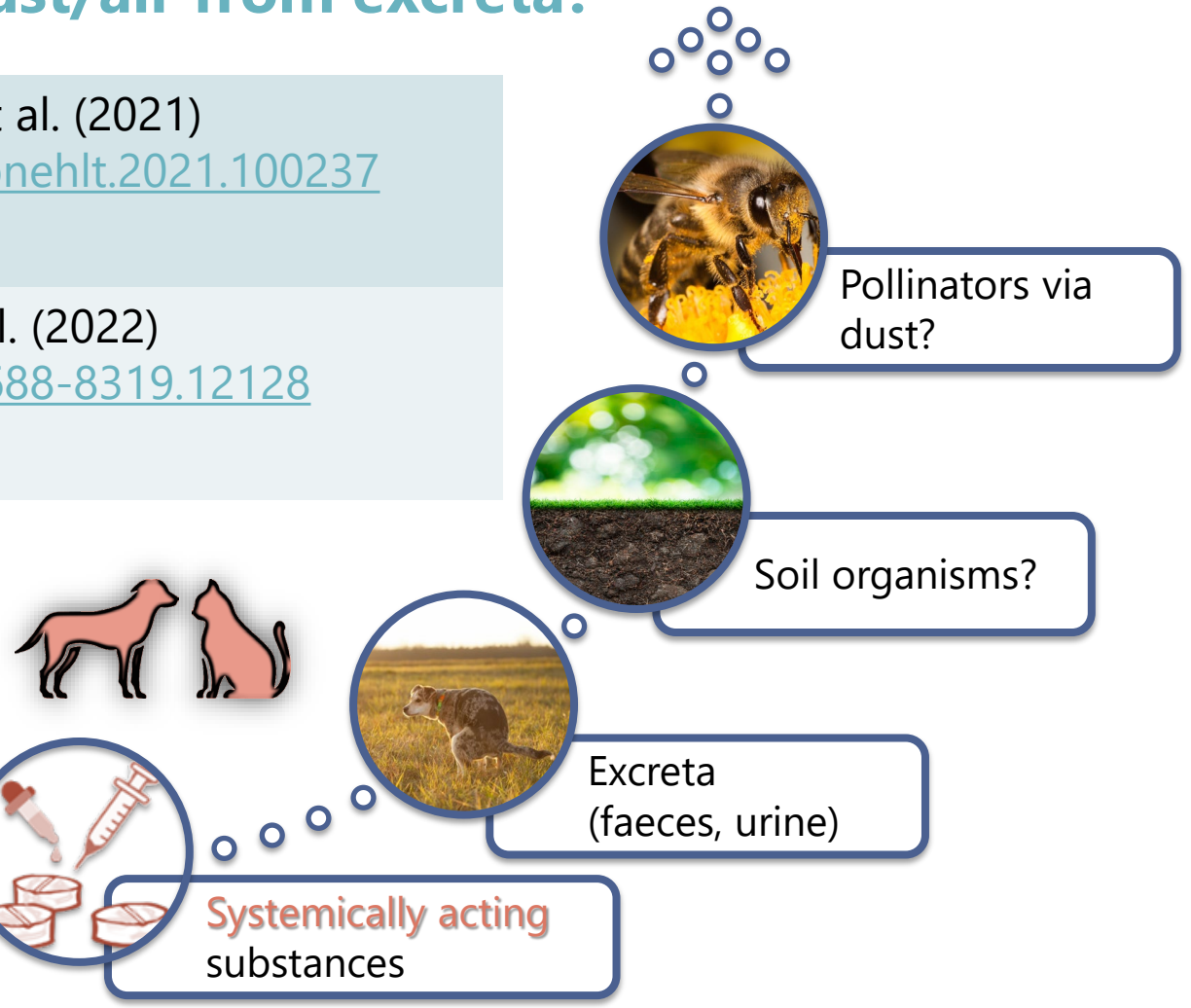
Terrestrial pathways poorly understood

Exposure of bees and pollinators via dust/air from excreta?

Exposure of bees and pollinators via dust/air from excreta or sludge of treated *livestock*?	Mahefarisoa et al. (2021) doi:10.1016/j.onehlt.2021.100237
The amounts of urine and faeces deposits in peri-urban ecosystems may be considerable.	De Frenne et al. (2022) doi:10.1002/2688-8319.12128

However…

- The **effects** of antiparasitic substances possibly present in the excreta in dogs or cats on terrestrial ecosystems have **not yet been studied**.



Terrestrial pathways poorly understood

Exposure of birds to contaminated dog hair used for nesting?

Exposure of birds to contaminated dog hair used for nesting?	Guldemond et al. (2019) https://www.clm.nl/publicaties/koolmezensterfte-en-buxusmotbestrijding/
Contamination of untreated dogs via secondary transfer from other dogs shown.	Diepens et al. (2023) doi:10.1016/j.scitotenv.2022.159550

However…

Neither importance nor the impact that the residues of antiparasitics from pets may have on wildlife are known.

Conclusions on environmental risks

… resulting from the use of ectoparasiticidal pet VMPs

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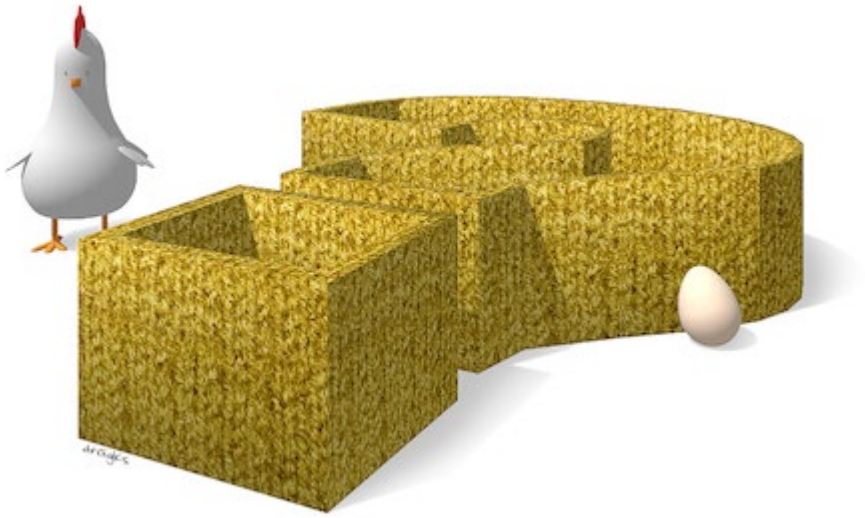
- Therefore, at present, it is **not possible**
  - **to elaborate** further **on environmental risks** arising from the use of **individual products** and substances with evidence or reasonable suspicion and, as a consequence,
  - to rank such products according to their environmental risks, **neither to generate substance-specific risk mitigation measures**.

- It is thus recommended to address those knowledge gaps.

And now?



Addressing knowledge gaps …

… for sound regulatory decisions and recommendations.

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- Specific ad-hoc monitoring studies (taylored for pet VMPs)
- Environmental fate & behaviour (closing data gaps for novel actives & PFASs)

Monitoring studies + fate & behaviour

Understanding exposure pathways

- Identification of environmental compartments at risk (and *potential adverse events*).
- Development of exposure models (PEC).

- ✓ Prescription status (Art. 34)
- ✓ Environmental warnings
- ✓ *"However clause"*
- ✓ Veterinary advice…

- Definition of *specific environmental concerns* in a regulatory context.
- Requirements for *product specific ERA*s and risk mitigation measures

EU Regulatory decisions

VICH GL 6 & 38

- Which companion animal VMPs would need a Phase II ?
- How should such a Phase II assessment look like ?

Take home messages

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- **General remarks**
  - The authorisation of a VMP is always based on a **positive overall benefit-risk balance**, (albeit for non-food producing animals environmental risks are currently not addressed).
  - **Bans and restrictions of substances** in certain (non-VMP) uses cannot be directly translated into **interpretations of monitoring data** due to extended transition periods, emergency uses, exemptions, imported contamination etc.
  - The **clear source apportionment** (biocide / pesticide / medicine) of measured environmental concentrations is therefore mostly **not possible**.
  - Don't only think of fipronil and imidacloprid and spot-ons! There are **40 different active substances** authorised in a multitude of ectoparasiticidal pet VMPs.

- **To allow for substantiated environmental risk assessments in the future**
  - **Specific ad-hoc monitoring studies** (taylored for pet VMPs), and
  - **Environmental fate & behaviour studies** in particular for "-laners" and other long-acting active substances and **PFAS** are essential.

Any questions?

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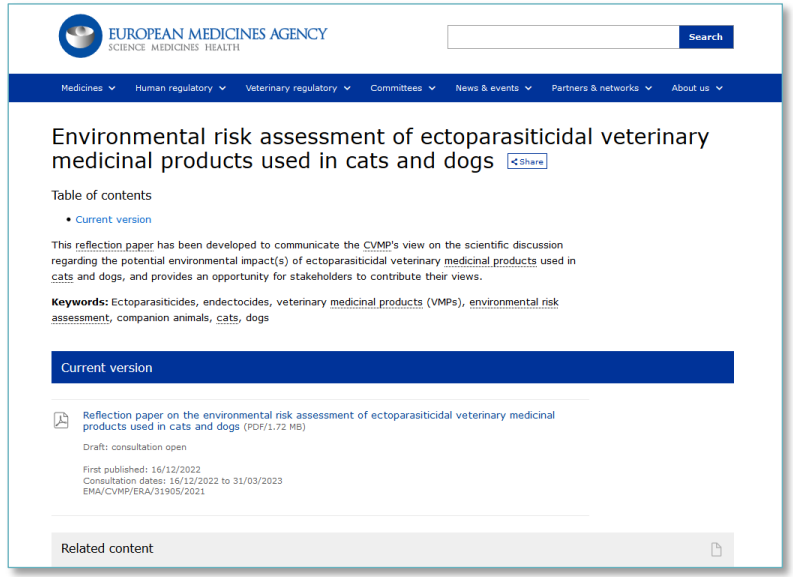
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Environmental risk assessment of ectoparasiticidal veterinary medicinal products used in cats and dogs

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This reflection paper has been developed to communicate the CVMP's view on the scientific discussion regarding the potential environmental impact(s) of ectoparasiticidal veterinary medicinal products used in cats and dogs, and provides an opportunity for stakeholders to contribute their views.

Keywords: Ectoparasiticides, endectocides, veterinary medicinal products (VMPs), environmental risk assessment, companion animals, cats, dogs

Current version

Reflection paper on the environmental risk assessment of ectoparasiticidal veterinary medicinal products used in cats and dogs (PDF/1.72 MB)

Draft: consultation open

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Related content

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Dipl.-Ing. Haru KRONEIS, MScTox, ERT

Institute for Marketing Authorisation of Medicinal Products & Lifecycle Management

Austrian Medicines Medicinal Devices Agency
BASG – Federal Office for Safety in Health Care
AGES – Austrian Agency for Health & Food Safety

Traisengasse 5 | A-1200 Vienna, Austria
T +43 (0)50555 36640 | M +43 (0) 664 884 755 93

haru.kroneis@ages.at | **www.basg.gv.at**