



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Environmental risk assessment for veterinary medicines

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Basic principles and current issues

EMA Veterinary Awareness Day 2023

Presented by Michael Empl on 12 September 2023  
V-EI-PHS



Source: Microsoft PowerPoint stock images

An agency of the European Union





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- Introduction
- Basic principles
- Summary
- Current issues





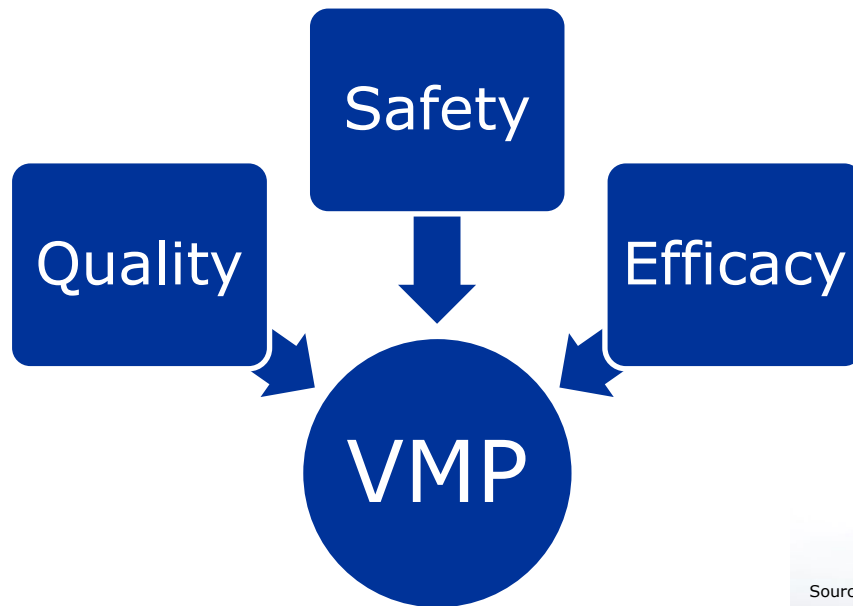
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- **Introduction**
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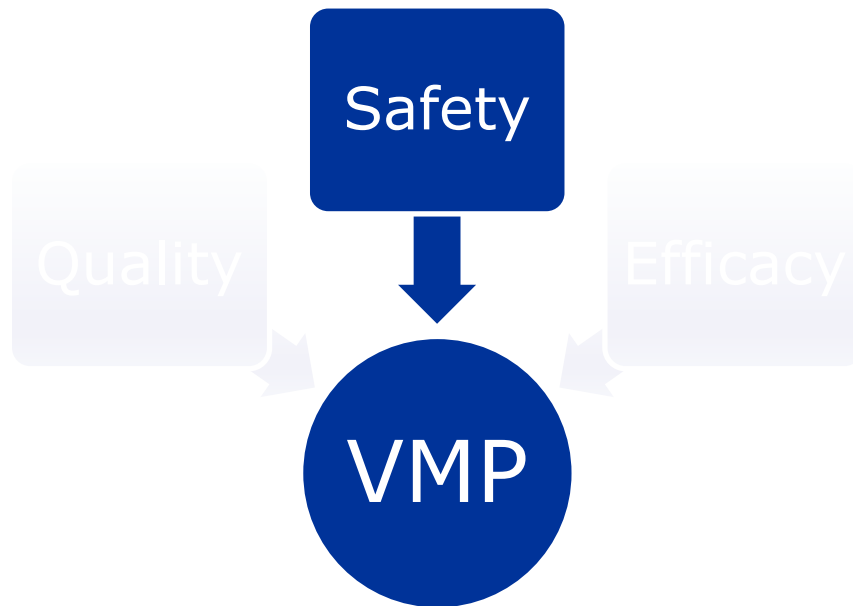
# Introduction — Aim of the veterinary medicinal product (VMP) authorisation process



Source: Microsoft PowerPoint stock images



## Introduction — Aim of the veterinary medicinal product (VMP) authorisation process



For the treated animal

For the user

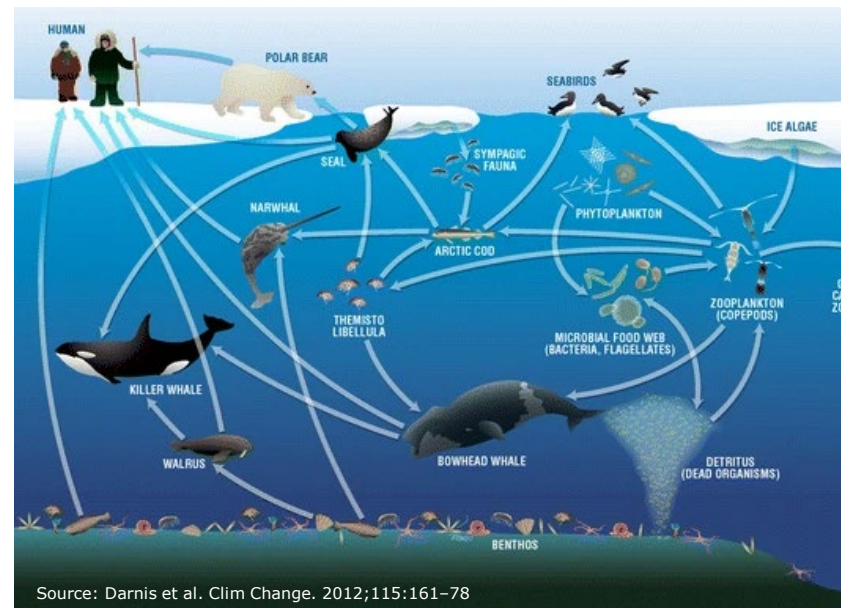
For the consumer

**For the environment**



# Introduction — Aim of the environmental risk assessment (ERA)

**Protection of the environment and ecosystems** (incl. public health)





## Introduction — VMPs in the environment

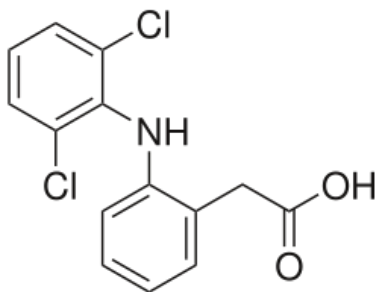
- 700–800 active substances are available for use in VMPs
- Unwanted effects on the environment possible, for instance (but not limited to):

<b>Class of VMP</b>	<b>Intended effect</b>	<b>Unintended effect on the environment</b>
Antimicrobials	Active against pathogenic bacteria	Active against "useful" bacteria in soil, water and sewage treatment plants (STPs)
Parasiticides	Active against pathogenic/unwanted endo- and ectoparasites	Active against non-target organisms (e.g. protozoans, insects, worms) in soil and water



## Introduction — Environmental incidents

- "Asian vulture crisis" in the 1990s–2000s\*
  - Population of vulture species endemic to the Indian subcontinent decreased up to 95%
  - Reason (only identified in 2004): Vultures had fed on carcasses of cattle treated with diclofenac
  - Cause of death: Renal failure → Visceral gout



Source: Shantanu Kuyeskar (CC BY-SA 4.0)

\* Oaks et al. Nature. 2004;427(6975):630–3





## Introduction — Environmental incidents

# THE SOCIAL COSTS OF KEYSTONE SPECIES COLLAPSE: EVIDENCE FROM THE DECLINE OF VULTURES IN INDIA\*

Eyal G. Frank<sup>1</sup> and Anant Sudarshan<sup>2</sup>

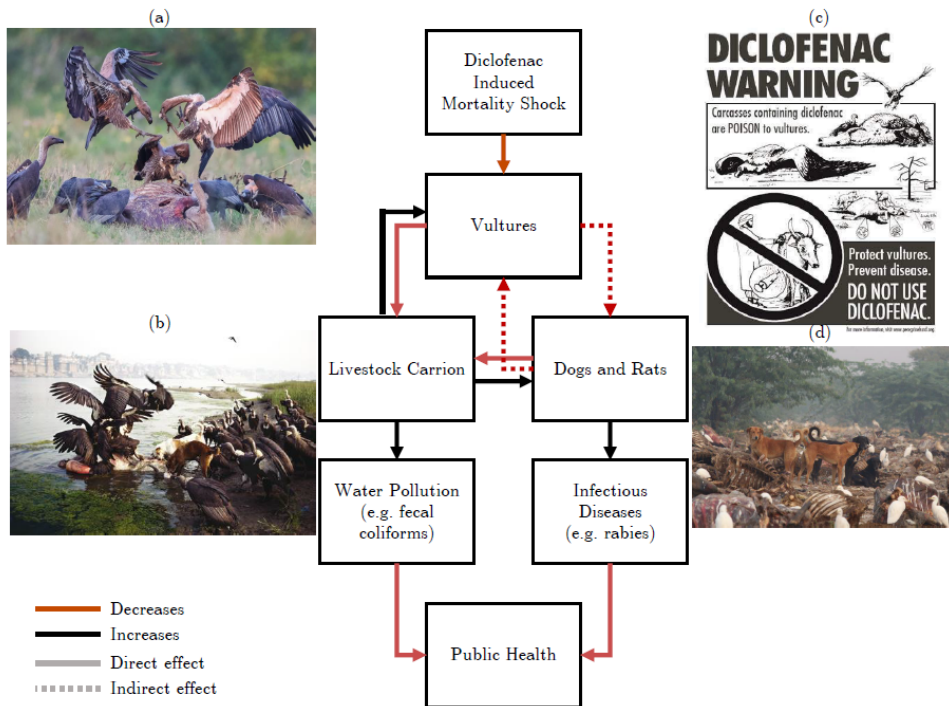
<sup>1</sup>*Harris School of Public Policy, University of Chicago. Keller Center, 1307 E 60th St.  
Chicago, IL 60637, USA. Email: eyalfrank@uchicago.edu*

<sup>2</sup>*Department of Economics, University of Warwick. Coventry, CV4 7AL, UK. Email:  
anant.sudarshan@warwick.ac.uk*

March 10, 2023



# Introduction — Environmental incidents



Source: EG Frank, A Sudarshan. The social costs of keystone species collapse: Evidence from the decline of vultures in India (working paper).  
[https://www.anantsudarsan.com/uploads/1/0/2/6/10267789/vultures\\_manuscript.pdf](https://www.anantsudarsan.com/uploads/1/0/2/6/10267789/vultures_manuscript.pdf) (accessed 8 September 2023)



# Introduction — Environmental incidents

NATURE | NEWS

## Cattle drug threatens thousands of vultures

Modelling study paints bleak picture for Europe's bird populations.

Rachel Becker

29 April 2016



*Ernil V. Lopez/Getty*

Eurasian griffon vultures, like these in Huesca, Spain, are threatened by veterinary use of diclofenac, researchers say.

Source: R. Becker. Cattle drug threatens thousands of vultures. Nature. 2016. DOI: 10.1038/nature.2016.19839



# Introduction — Environmental protection initiatives in the EU

## COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL

European Union

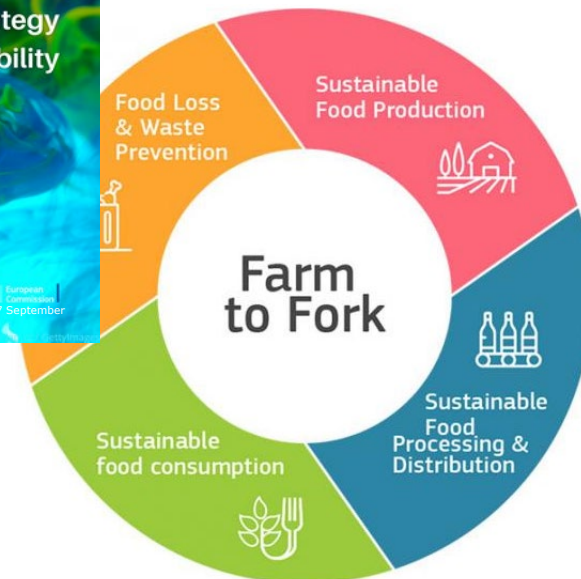


**A European Green Deal**  
Striving to be the first climate-neutral continent

Source: European Commission ([https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/european-green-deal\\_en](https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/european-green-deal_en); accessed 7 September 2023)



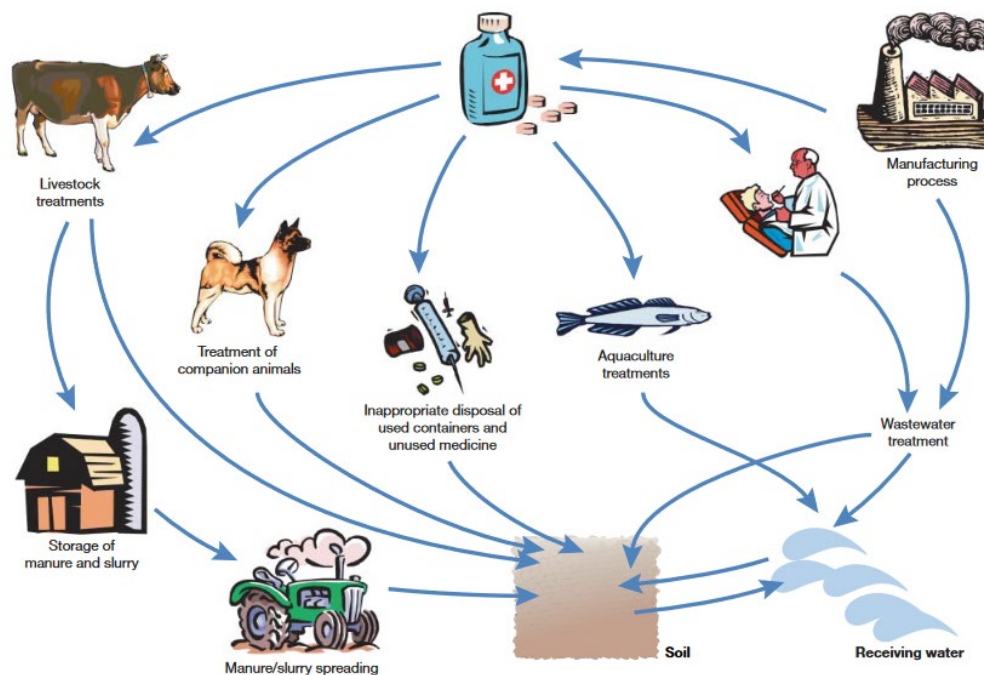
Source: European Commission ([https://environment.ec.europa.eu/strategy/zero-pollution-action-plan\\_en](https://environment.ec.europa.eu/strategy/zero-pollution-action-plan_en); accessed 7 September 2023)



Source: European Commission ([https://food.ec.europa.eu/horizontal-topics/farm-fork-strategy\\_en](https://food.ec.europa.eu/horizontal-topics/farm-fork-strategy_en); accessed 7 September 2023)



# Introduction — Environmental entry routes for medicines



Source: ABA Boxall. EMBO Rep. 2004;5(12):1110-6. DOI: 10.1038/sj.embor.7400307.



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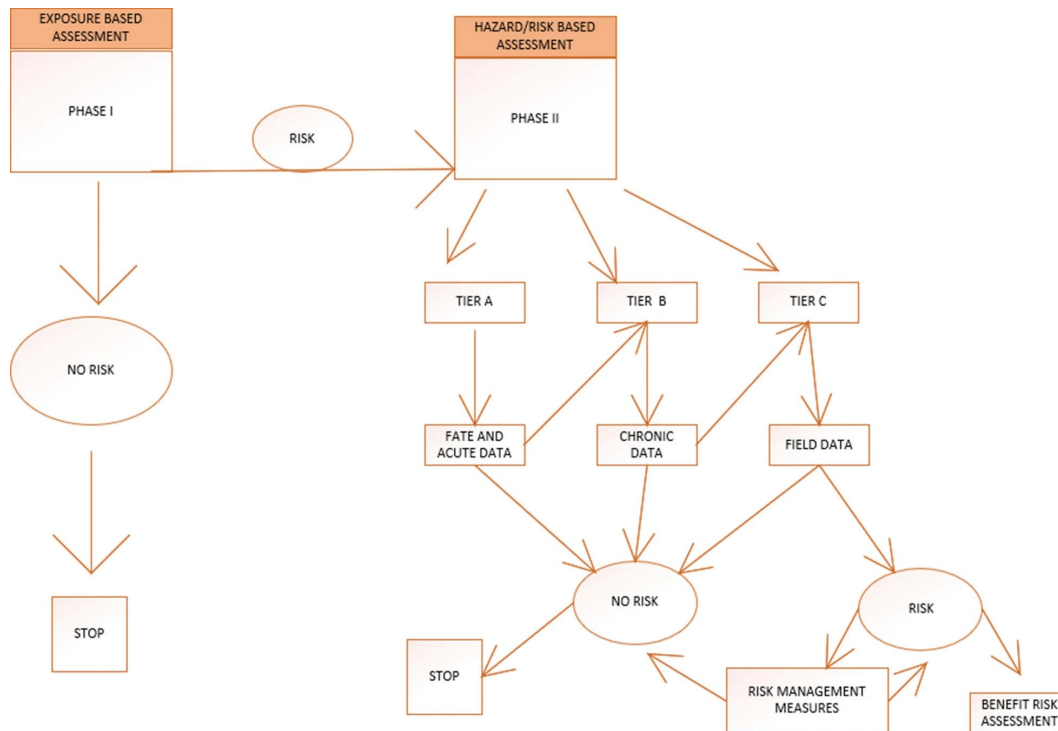
## Basic principles of ERA for VMPs — Legal basis

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

- An ERA is **mandatory** for **all applications** (with very few exceptions)
- An ERA shall be conducted in **two phases**, of which the **first shall always be performed**
- An **unacceptable risk** to the environment can lead to **non-authorisation** of a VMP (unlike for human medicines)
- The basic process to follow is described in internationally harmonised and EMA guidance documents (e.g. VICH GL6 [→ phase I) and VICH GL38 [→ phase II])



# ERA for VMPs — A tiered approach



Source: Fabrega, Carapeto. Environ Sci Eur. 2020;32:99





## Basic principles of ERA for VMPs — Risk determination



$$\text{RISK} = \text{HAZARD} \times \text{EXPOSURE}$$

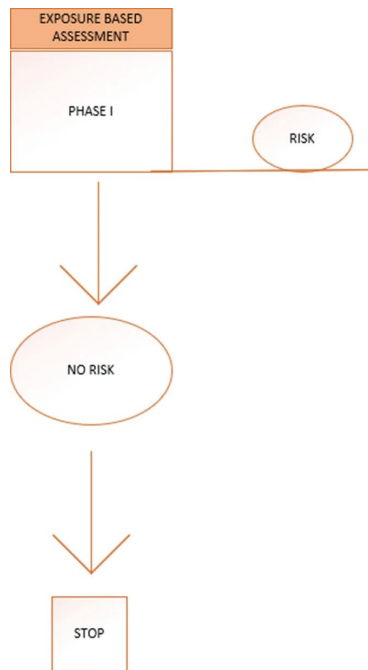
Probability of something "bad" happening

How dangerous is it?

How long/much have I been in contact with it?



# ERA for VMPs — Exposure-based assessment (phase I)



Source: Fabrega, Carapeto. Environ Sci Eur. 2020;32:99



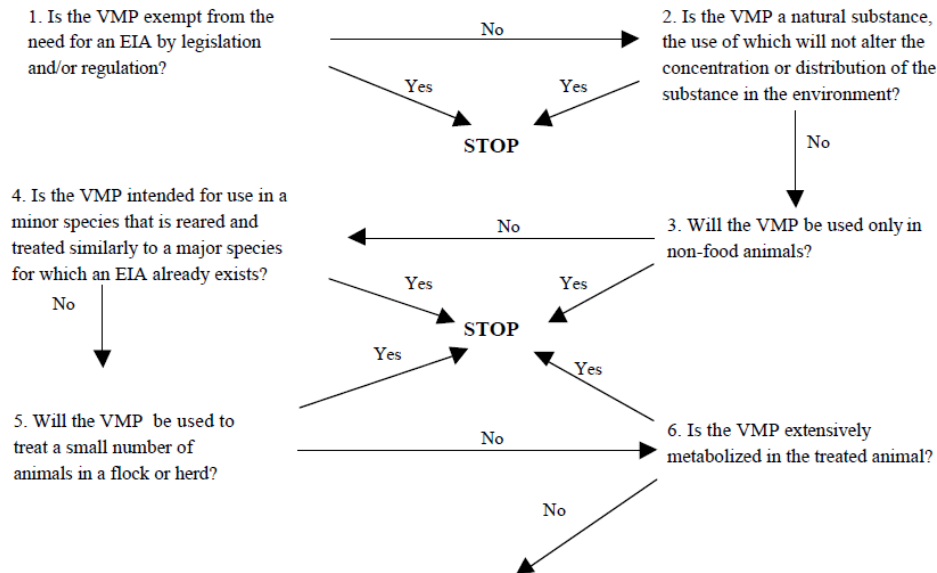
## ERA for VMPs — Exposure-based assessment (phase I)

- Main question to answer: **How high is the exposure?**
- Decision tree with **qualitative** (*e.g. on target species or pattern of use*) and **quantitative** (*i.e. is the exposure higher than certain "safe" trigger values?*) questions
- Basic worst-case assumptions (e.g. the full dose given to the animal will be excreted into the environment) that allow for a first evaluation of the environmental risk associated with the use of a VMP



# ERA for VMPs — Phase I qualitative questions

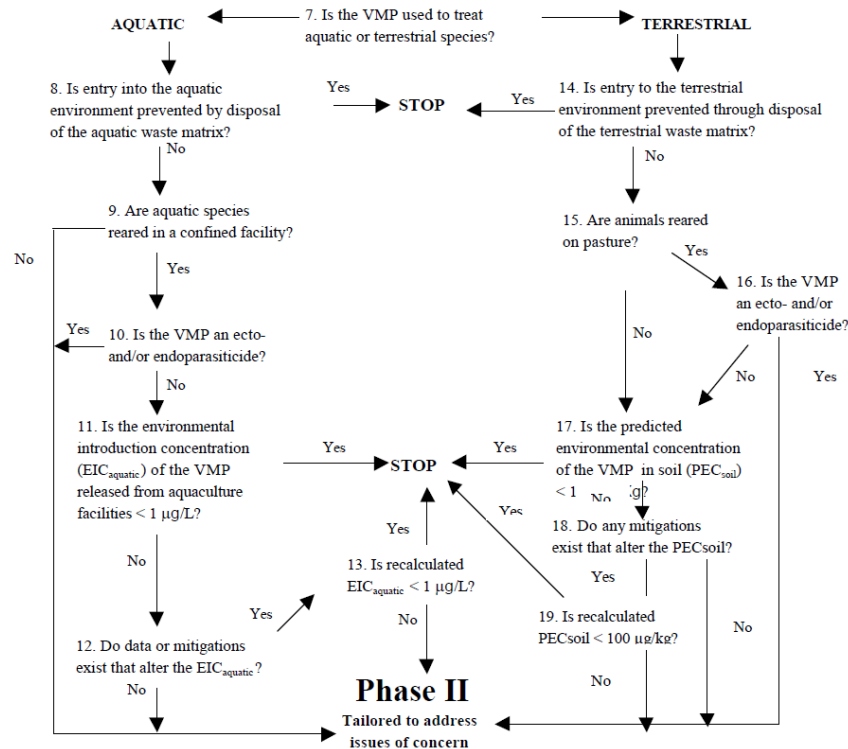
**Figure 1. Phase I Decision Tree**



Source: VICH GL6. Environmental impact assessment (EIAS) for veterinary medicinal products — Phase I (CVMP/VICH/592/98-FINAL). 2000.



# ERA for VMPs — Phase I quantitative questions



Source: VICH GL6. Environmental impact assessment (EIAS) for veterinary medicinal products — Phase I (CVMP/VICH/592/98-FINAL). 2000.

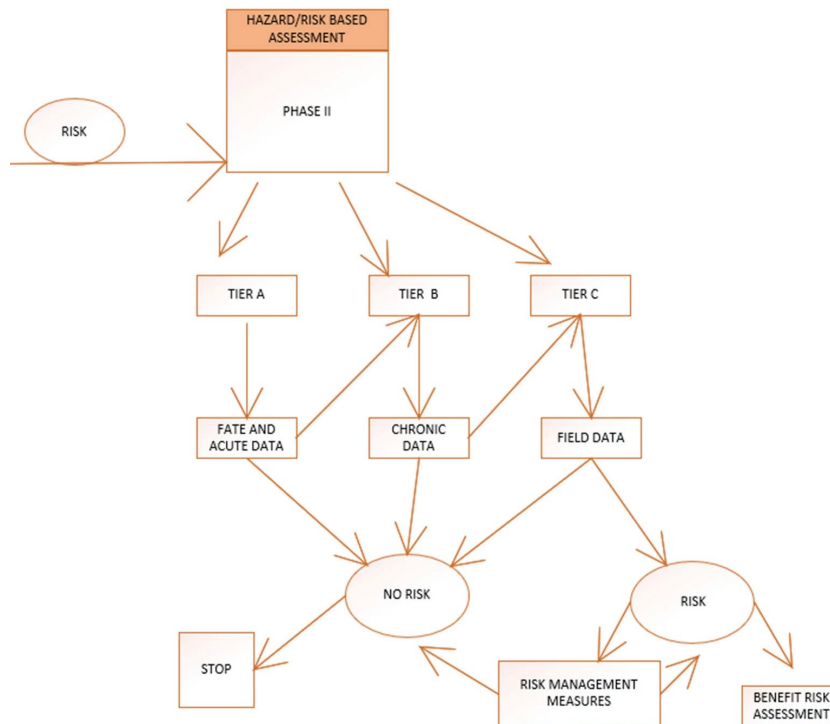


## ERA for VMPs — Exposure-based assessment (phase I)

- Main question to answer: **How high is the exposure?**
- Decision tree with **qualitative** (*e.g. on target species or pattern of use*) and **quantitative** (*i.e. is the exposure higher than certain "safe" trigger values?*) questions
- Basic worst-case assumptions that allow for a first evaluation of the environmental risk associated with the use of a VMP
- The exceedance of a trigger value indicates a potential risk → More in-depth assessment necessary (phase II ERA)



# ERA for VMPs — Hazard/risk-based assessment (phase II)



Source: Fabrega, Carapeto. Environ Sci Eur. 2020;32:99



## ERA for VMPs — Hazard/risk-based assessment (phase II)

- Main question to answer: **How dangerous is the VMP in question and what can be done about it?**
- Collection of experimental/"real-world" data to get information about the VMP's behaviour/fate in the environment and to define levels at which the VMP does or does not induce toxicity in non-target organisms
- Testing gets more complex/"realistic" from tier to tier, if needed
- At each tier, it is determined whether the environmental exposure is below toxicity-inducing levels → Calculation of the "Risk Quotient" (RQ)
- $RQ = \frac{Exposure}{Non-toxic\ level} = \text{below } 1 \text{ ("no risk")} \text{ or above } 1 \text{ ("risk")}$
- If a risk is identified, the ERA progresses to next higher tier/benefit-risk assessment





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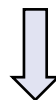
# Basic principles of ERA for VMPs — Summary

Phase I — Exposure assessment



Decision on whether phase II ERA is necessary

Phase II "tier A" — Collection of experimental data



Decision on whether further assessment is necessary (RQ > 1 or < 1?)

Phase II "tier B (and C)" — Further collection of experimental data



Risk assessment/risk mitigation

If the RQ is still > 1, the risk is not acceptable, and the VMP cannot be authorised



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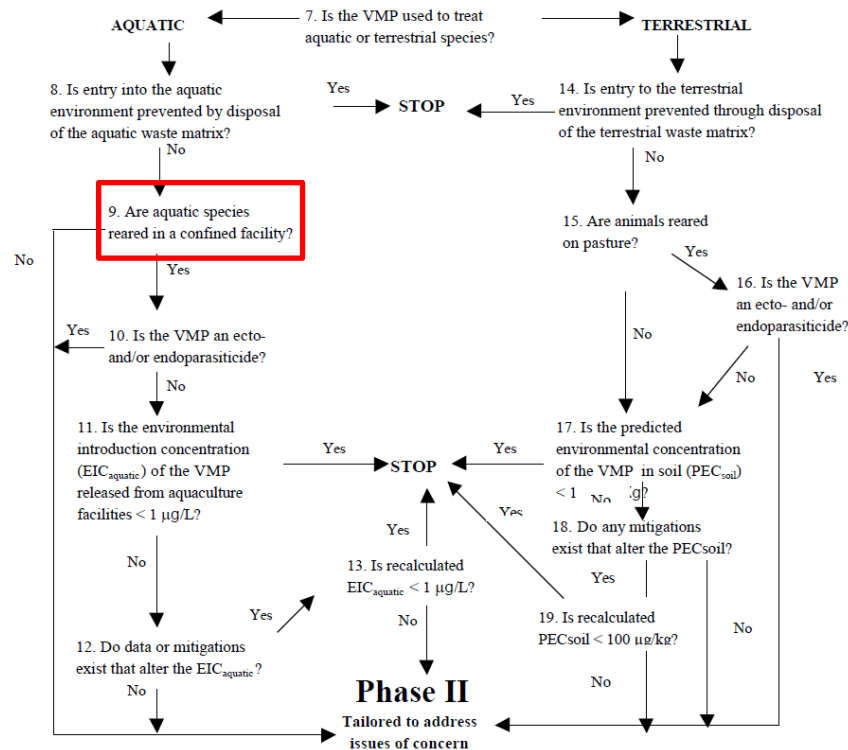


## Current issues — ERA for VMPs used in aquaculture

- Growth of the aquaculture sector expected in the coming years, which might only be achievable through the use of VMPs
- The farming of fish may have a considerable impact on the environment and ecosystems
- The number of VMPs available for use in aquaculture is extremely low → Off-label use



# Current issues — ERA for VMPs used in aquaculture



Source: VICH GL6. Environmental impact assessment (EIAS) for veterinary medicinal products — Phase I (CVMP/VICH/592/98-FINAL). 2000.



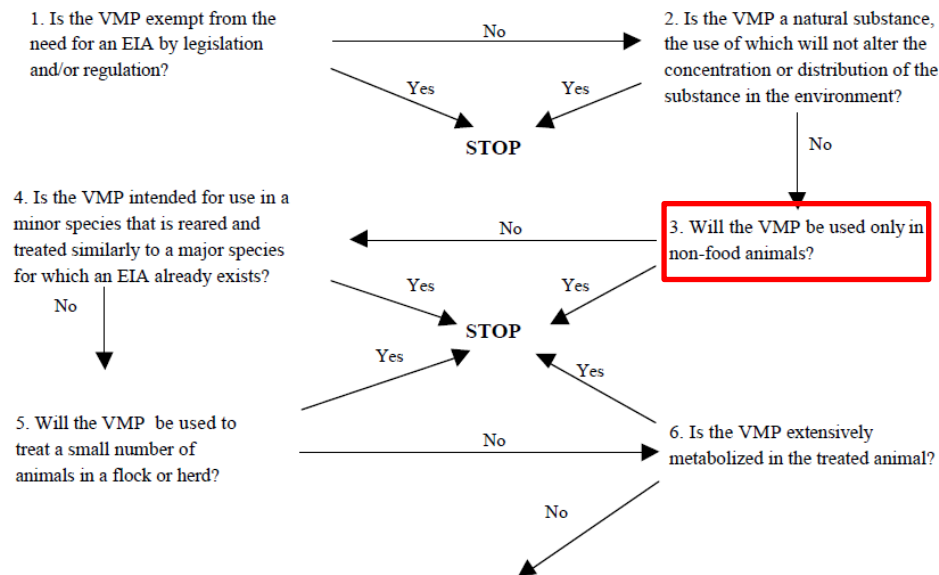
## Current issues — ERA for VMPs used in aquaculture

- Growth of the aquaculture sector expected in the coming years, which might only be achievable through the use of VMPs
- The farming of fish may have a considerable impact on the environment and ecosystems
- The number of VMPs available for use in aquaculture is extremely low → Off-label use
- Currently, no specific guidance on how to perform an ERA for VMPs for use in aquaculture is available
- To increase availability, harmonisation and environmental protection, CVMP/ERAWP is currently developing a specific "ERA for aquaculture" guideline



# Current issues — Parasiticides for cats and dogs

**Figure 1. Phase I Decision Tree**



Source: VICH GL6. Environmental impact assessment (EIAS) for veterinary medicinal products — Phase I (CVMP/VICH/592/98-FINAL). 2000.

# Current issues — Parasiticides for cats and dogs



Science of The Total Environment

Volume 755, Part 1, 10 February 2021, 143560




Science of The Total Environment



Volume 858, Part 1, 1 February 2023, 159550



## Potential role of veterinary flea products in widespread pesticide contamination of English rivers

Rosemary Perkins<sup>a</sup>  , Martin Whitehead<sup>b</sup>, Wayne Civil<sup>c</sup>, Dave Goulson<sup>a</sup>



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<https://doi.org/10.1016/j.scitotenv.2020.143560> 

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## Pet dogs transfer veterinary medicines to the environment

N.J. Diepens, D. Belgers, L. Buijse, I. Roessink  


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<https://doi.org/10.1016/j.scitotenv.2022.159550> 

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▲ Research found chemical fipronil in 99% samples from 20 rivers in England. Photograph: Danny Lawson/PA

Highly toxic insecticides used on cats and dogs to kill fleas are poisoning rivers across England, a study has revealed. The discovery is “extremely concerning” for water insects, and the fish and birds that depend on them, the scientists said, who expect significant environmental damage is being done.





# Thank you for your attention!

## Any questions?

### Further information

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