



Veterinary
Medicines
Directorate

Reflections on the environmental risks resulting from topical spot-on ectoparasiticides when used as veterinary medicines for dogs



Presented by: Jason Weeks and Ken Stapleton
Date: 28th September 2018

What are topical spot-on ectoparasiticides?

- Used in veterinary medicine to control parasites
 - such as fleas, ticks, worms on domesticated animals.
- Share the market with products such as dips, powders, sprays and collars.
- Applied between the shoulder blades or striped down the back of the animal,
 - limiting licking the product off.



What are topical spot-on ectoparasiticides?

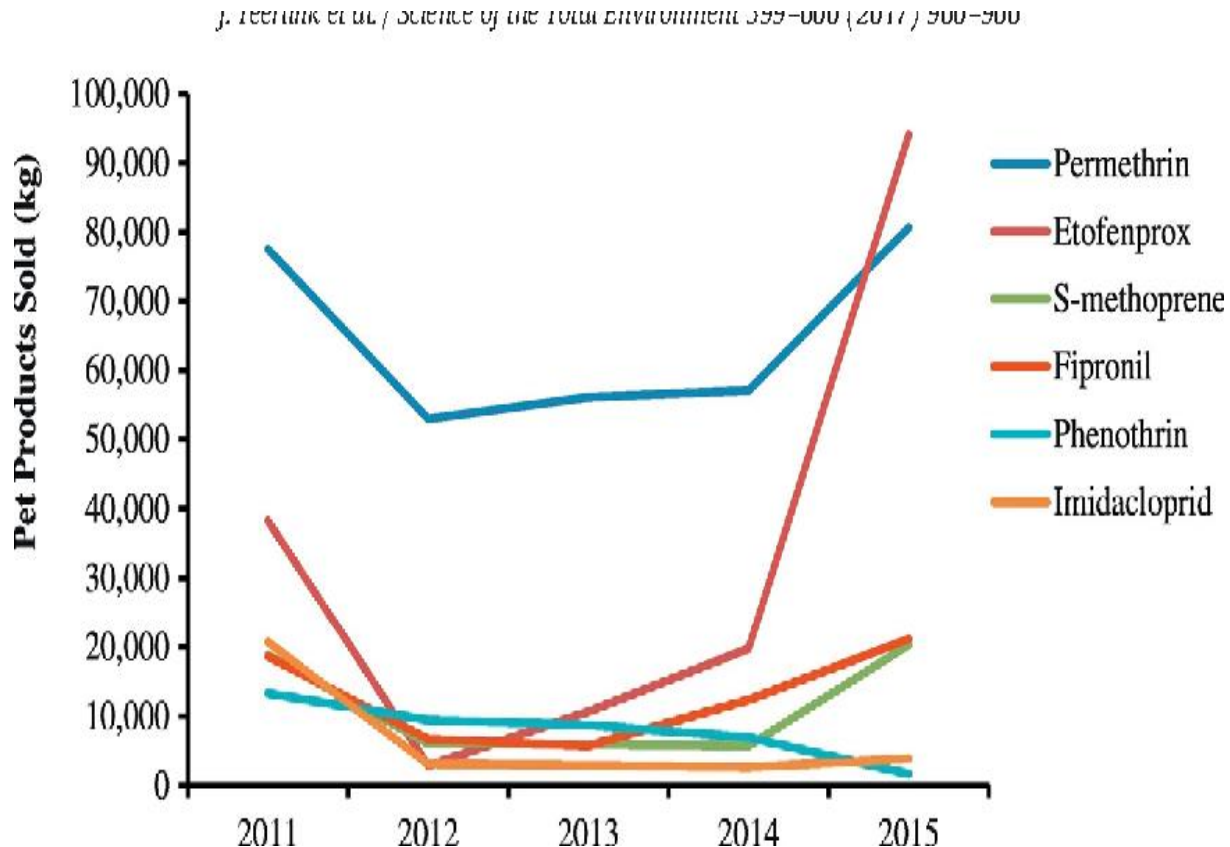
- Generally, little systemic absorption in the dog
- Distributed over the entire skin surface of the dog as rapidly as 12 hours following application.
 - Such distribution throughout the lipid layers of the skin:
 - provides for prolonged effectiveness;
 - and resistance to loss of efficacy as a result of bathing or wetting.
- Most products are reapplied at frequent intervals.
 - *“For optimal control of flea and/or tick infestation the treatment schedule can be based on the local epidemiological situation.*
 - *In the absence of safety studies, the minimum treatment interval is 4 weeks.”*

Combinations of active substances used in spot-ons

Active Ingredients	Chemical Groups
(S)-methoprene, eprinomectin, fipronil, praziquantel	Phenylpyrrazole, avermectin, phenylpyrrazole, pyrazinoisoquinoline deriv.
(S)-methoprene, fipronil	Phenylpyrrazole, phenylpyrrazole
Deltamethrin	Pyrethroid
Dinotefuran, permethrin (40:60), pyriproxyfen	Neonicotinoid, pyrethroid, pyridine
Dinotefuran, pyriproxyfen	Neonicotinoid, pyridine
Emodepside, praziquantel	Depsipeptide, pyrazinoisoquinoline derivative
Fipronil	Phenylpyrrazole
Fipronil, permethrin (Cis:Trans 25:75 or 40:60)	Phenylpyrrazole, pyrethroid
Fipronil, pyriproxyfen	Phenylpyrrazole, pyridine
Fluralaner	Isoxazoline-subs. benzamide deriv.
Fluralaner, moxidectin	Isoxazoline-subs. benzamide deriv., milbemycin
Imidacloprid	Neonicotinoid
Imidacloprid, moxidectin	Neonicotinoid, milbemycin
Imidacloprid, permethrin (Cis:Trans 40:60)	Neonicotinoid, pyrethroid
Indoxacarb	Oxadiazine
Indoxacarb, permethrin (Cis:Trans 40:60)	Oxadiazine, pyrethroid
Permethrin (Cis:Trans 25:75 or 40:60)	Pyrethroid
Praziquantel	Pyrazinoisoquinoline derivative
Selamectin	Avermectin

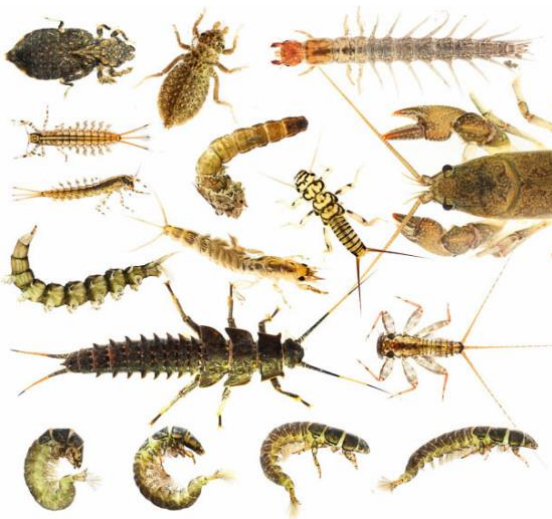
Ectoparasiticides as pet products: Sales

- Kg sold per year of the top six pesticides found in pet products from 2011 to 2015 (US data).



Ectoparasiticides: Specific ecotoxicity concerns

- Pharmacologically active against non-target organisms that are biologically related to the target pathogen.
 - Potential for neurotoxic and growth regulation effects
 - Little information is available on the actual impact of these pesticides on those species likely to be exposed to them, in the field setting.



Neonicotinoids and fipronil: A short history

- Neonicotinoids and fipronil are relatively new, widely used, compounds originally designed as plant protection products.
- Highly persistent in soils, and tend to accumulate in soils and sediments and have been detected frequently in the global environment
 - (Bonmatin *et al.* 2014).
- Recently, have accounted for approximately a third of the world insecticide market;
 - annual world production of the archetype neonicotinoid, imidacloprid, was estimated to be 20,000 tonnes in 2010.

Neonicotinoids & fipronil: Concern?



Neonicotinoid Insecticides in British Freshwaters

2016 Water Framework Directive Watch List
Monitoring Results and Recommendations

14th December 2017
Matt Shardlow

[Updated with Northern Ireland results
10th December 2017]

Saving the small things that run the planet

Conclusions of the Worldwide Integrated Assessment on the risks of neonicotinoids and fipronil to biodiversity and ecosystem functioning

J. P. van der Stuijts • V. Amaral-Rogers • L. P. Belzunces • M. F. I. J. Bijleveld van Lexmond •
J.-M. Bonmatin • M. Chagnon • C. A. Downs • L. Furlan • D. W. Gibbons • C. Glorio •
V. Girolami • D. Goulson • D. P. Kreutzweiser • C. Krupke • M. Liess • E. Long • M. McField •
P. Mineau • E. A. D. Mitchell • C. A. Morrissey • D. A. Noome • L. Pisa • J. Settele •
N. Simon-Delso • J. D. Stark • A. Tapparo • H. Van Dyck • J. van Praagh • P. R. Whitehorn •
M. Wiemers

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Effects of neonicotinoids and fipronil on non-target
invertebrates

L. W. Pisa, corresponding author V. Amaral-Rogers, L. P.
Belzunces, J. M. Bonmatin, C. A. Downs, D. Goulson, D. P.
Kreutzweiser, C. Krupke, M. Liess, M. McField, C. A. Morrissey,
D. A. Noome, J. Settele, N. Simon-Delso, J. D. Stark, J. P. Van der
Sluijs, H. Van Dyck, and M. Wiemers

Department for Environment, Food and Rural Affairs

Neonicotinoid insecticides and bees

The state of the science and the regulatory response

Date: 13 September 2012



Department of Pesticide Regulation
Environmental Monitoring Branch
Surface Water Protection Program
1001 I Street
Sacramento, California 95812

Review of the Environmental Fate and Use Patterns of Fipronil in California

Jennifer Teerlink, Ph.D.

June 22, 2017

Background

This document is intended as a supplement to the Department of Pesticide Regulation's (DPR's) 2007 environmental fate review of fipronil (Gunasekara et al., 2007). More recent journal articles addressing national use trends, environmental fate, and impact to non-target organisms have recently been published (Bonmatin et al., 2015; Pisa et al., 2015; Simon-Delso et al., 2015). A comprehensive summary of California monitoring data and relative toxicity has also been documented (Budd et al., 2015). Finally, the fipronil occurrence and fate of fipronil through the wastewater treatment process has been reported (Sadaria et al., 2017). Herein, key findings are summarized; however, for a more in depth discussion of specific topics each of the above studies should be referenced.

Introduction

Fipronil (5-amino-1[2,6-dichloro-4-(trifluoromethyl)phenyl]-4[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile) is a phenylpyrazole insecticide first synthesized by Rhone-Poulenc Ag Company (now Bayer Crop Science) in 1987 (Council, 2000) and registered for use in the United States in 1996. The insecticide controls a broad spectrum of insects at larval and adult stages by inhibiting the nervous system by binding to the GABA receptors and to glutamate receptors coupled to chloride channels (Simon-Delso et al., 2015). As of May 2017, there were 134 fipronil products registered for use in the state of California, 92 of which are formulated in

Fipronil washoff to municipal wastewater from dogs treated with spot-on products.

Jennifer Teerlink, Jorge Hernandez, Robert Budd

Published 2017 in The Science of the total environment

Neonicotinoids & fipronil: EU Commission ruling

- Outdoor use of neonicotinoids restricted
 - limited to greenhouses, despite some environmental groups having reservations about the chemicals leaching into water supplies.
 - Other neonicotinoids, such as thiacloprid, will continue to be exempt from the ban.



Science & Environment

EU member states support near-total neonicotinoids ban

By Matt McGrath
Environment correspondent

27 April 2018



EU agrees total ban on bee-harming pesticides

The world's most widely used insecticides will be banned from all fields within six months, to protect both wild and honeybees that are vital to crop pollination



Neonicotinoids and fipronil: Continuing use

- A wide variety of applications,
 - including the most common prophylactic application by seed coating.



- As a result of their use and fate properties, they are found in all environmental compartments including soil, water and air.

Neonicotinoids & fipronil: Mechanism of action

- Neonicotinoids disrupt neural transmission in the CNS of invertebrates and mimic the action of neurotransmitters.
- Fipronil inhibits neuronal receptors, continuously stimulate neurons leading to death of target invertebrates.
- Synergistic effects with other stressors are documented.
- Both compound and metabolites can be toxic.
 - Resulting in prolonged toxicity?
 - Lethal and sub-lethal impacts on non-target organisms, including insect predators and vertebrates?

Neonicotinoids & fipronil: Concern?

- Considering their:
 - mode of action,
 - the systemic properties in plants,
 - environmental fate characteristics: Persistence
- Coupled with limited information about the toxicity profiles of these compounds and their metabolites, neonicotinoids and fipronil may present significant risks to the environment.

Buglife report

- “*Systematic testing of neonicotinoids in rivers in 2016*”
 - UK Environment Agency data
 - Limited sampling
 - 23 rivers tested (absent in only 6)
 - Issues concerning detection limits, etc
 - No Environmental Quality Standard defined (‘safe limit’)
- Imidacloprid detected in a remote stream in Cairngorms
- Consideration as an emerging pollutant by the EA



Neonicotinoid Insecticides in British Freshwaters

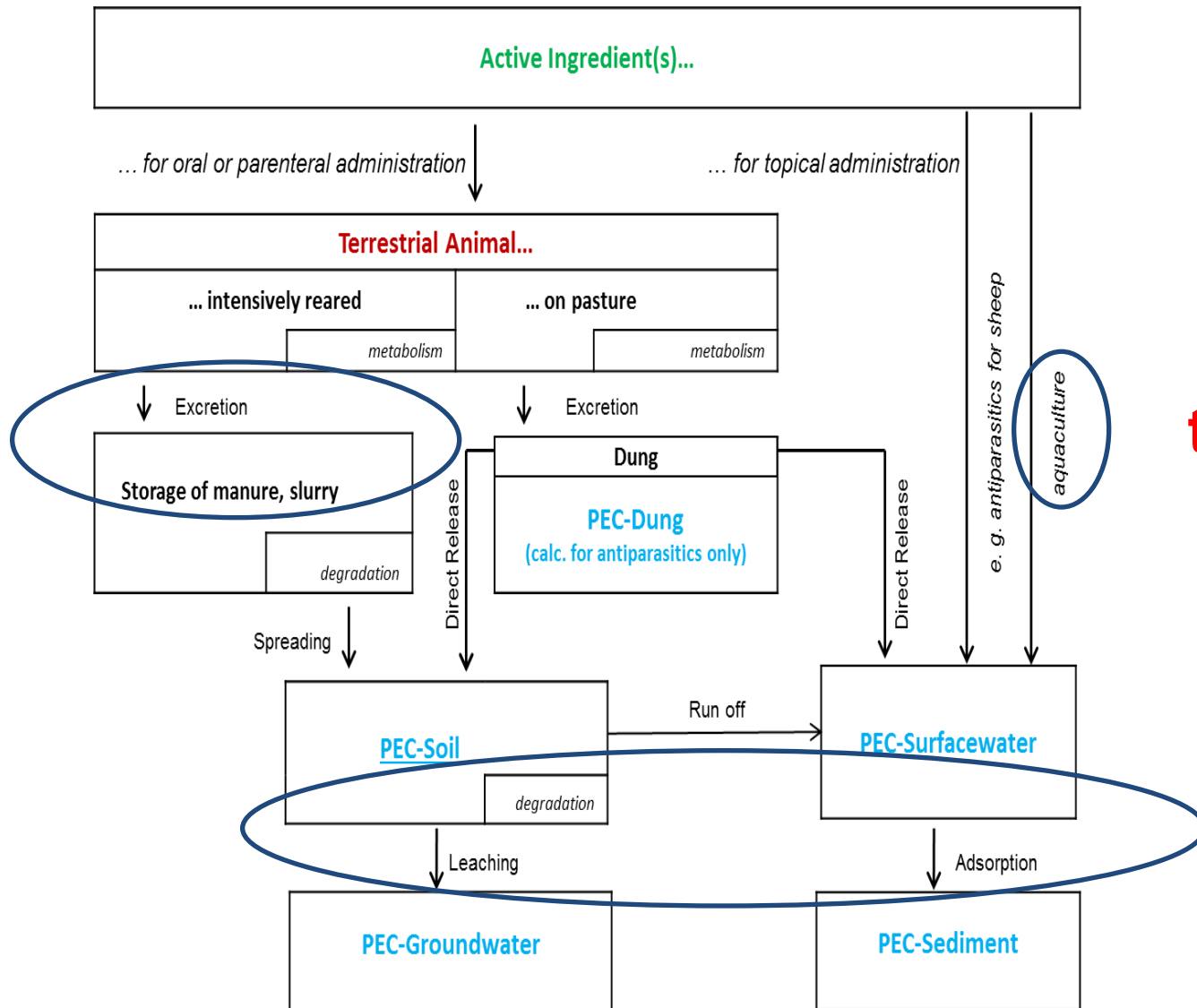
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Saving the small things that run the planet

Exposure pathways of veterinary medicines

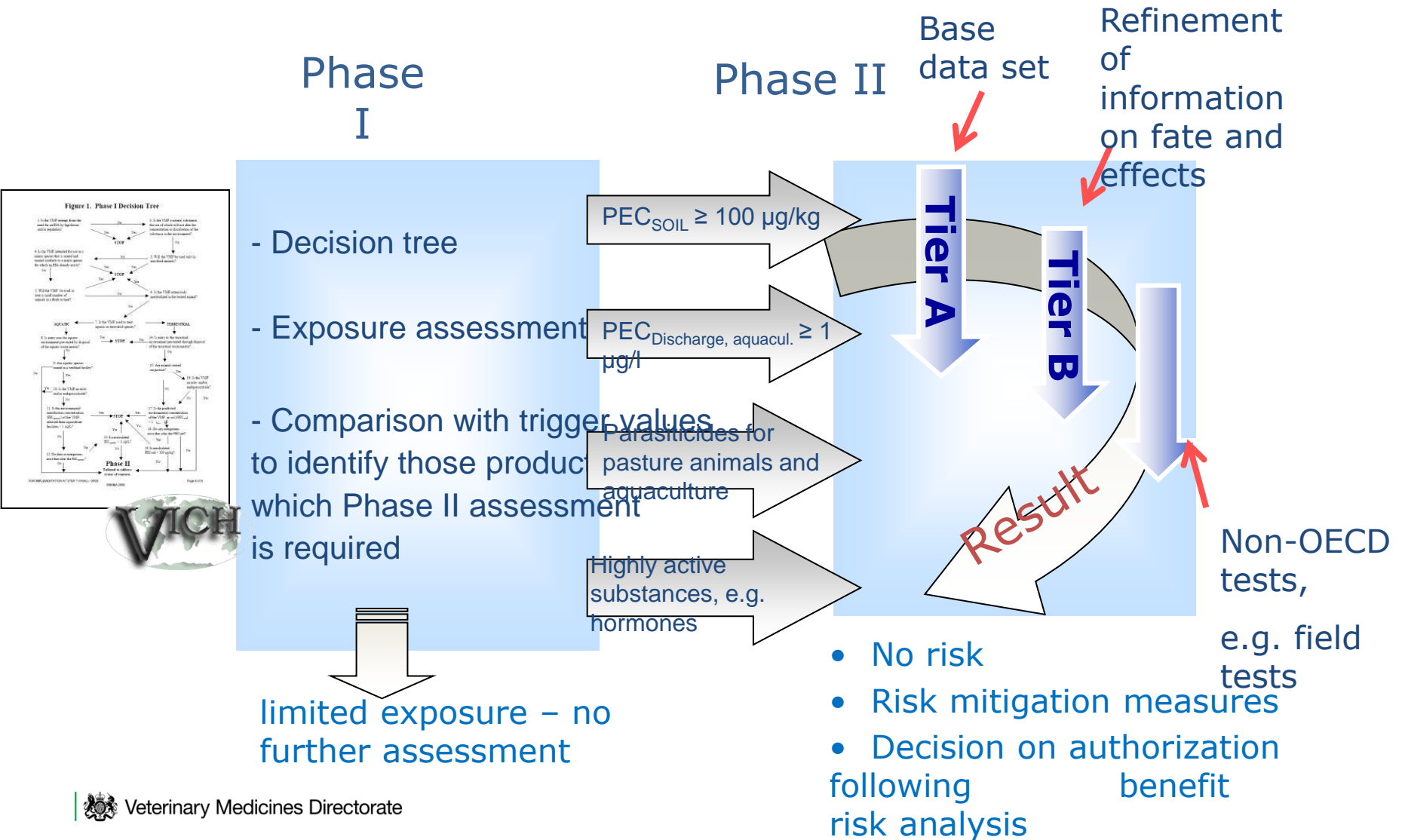


**Waste
water
treatment
plants
?**



Current environmental risk assessment process

- VICH and CVMP guidance



Measured exposure and toxicity endpoint values

- Summary of toxicity and wastewater effluent concentrations reported for pesticides found in pet products (US data)

Compound	Aquatic invertebrates ^a		Wastewater effluent (ng/L)
	Acute (ng/L)	Chronic (ng/L)	
Fipronil	110	11	14-49 ^b
Fipronil sulfide	1065	110	1.3-2 ^b
Fipronil desulfinyl	100,000	10,300	<0.39-1.2 ^b
Fipronil sulfone	360	37	1.1-16.3 ^b
Fipronil amide	—	—	<0.2-4.1 ^b
Permethrin	10.6	1.4	ND-170 ^c
Etofenprox	400	170	NA
S-methoprene	16,500	51,000	NA
Phenothrin	2200	470	NA
Imidacloprid	34,500	1050	83-305 ^b

^a USEPA Aquatic Life Benchmarks (USEPA, 2014b).

^b (Sadaria et al., 2016b).

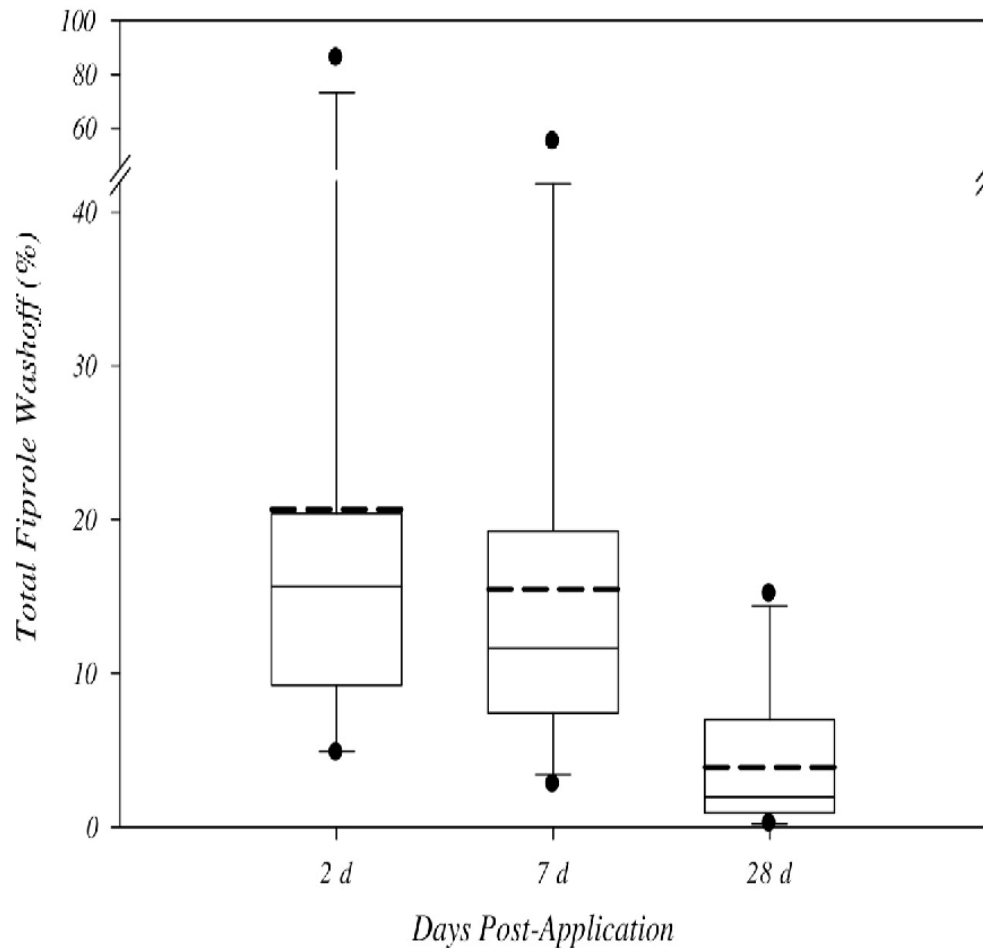
^c (Markle et al., 2014).

Fipronil: Measured concentrations in WWTPs following use as a veterinary medicine

- Fipronil and degradates reported in treated wastewater effluent, concentrations > USEPA Aquatic Life Benchmarks, indicates a risk to the surface waters to which they discharge.
- Volunteers treated their dogs with a fipronil-containing spot-on product. Dogs were washed either 2, 7, or 28 days after product application, and rinsate from 34 discrete bathing events were analysed by LC-MS/MS for fipronil and fiproles.

Fipronil: Measured concentrations in WWTPs following use as a veterinary medicine

- Percent wash-off of total fiproles as a function of time.





Fipronil: Measured concentrations in WWTPs following use as a veterinary medicine

- The active ingredients contained in spot-on and other pet products (i.e., shampoos, sprays) enter wastewater catchments through dog bathing activities, posing a potential risk to the aquatic organisms downstream of wastewater discharge
- Comparisons of mass loading calculated using California sales data and recent wastewater monitoring suggest fipronil-containing spot-on products as potentially important source of fipronil to wastewater treatment systems in California.

Fipronil & neonicotinoids: Other potential sources


Wash off of imidacloprid and fipronil from turf and concrete surfaces using simulated rainfall.

 Dang Quoc Thuyet, Brant C Jorgenson, Christopher Wissel-Tyson, Hirozumi Watanabe, Thomas M Young

 Published 2012 in The Science of the total environment

Environmental fate and exposure; neonicotinoids and fipronil

 J.-M. Bonmatin, Clemente Giorio, +10 authors Andrea Tapparo

 Published 2015 in Environmental science and pollution research...

Systemic insecticides (neonicotinoids and fipronil): trends, uses, mode of action and metabolites

 Noa Simon-Delso, Vanessa Amaral-Rogers, +26 authors Martin Wiemers

 Published 2015 in Environmental science and pollution research...

Risk Mitigation: Clarity and communication

INDICATION: In the absence of safety studies, the minimum treatment interval is 4 weeks.

■ **SPECIAL STORAGE PRECAUTIONS** : Keep out of the reach and sight of children. Store below 30°C. Store in a dry place. Store in the original package. Do not use after the expiry date stated on the carton and pipette after "EXP".

■ **SPECIAL WARNINGS** : **Special warnings for each target species** : Shampooing an hour prior to treatment does not affect the efficacy of the product against fleas. Bathing/immersion in water within two days after application of the product should be avoided. Weekly immersion in water for one minute reduces the period of persistent insecticidal efficacy against fleas by one week. The product does not prevent ticks from attaching to the animals. If the animal has been treated prior to exposure to the ticks, the ticks will be killed in the first 24-48 hours after attachment. This will usually be prior to engorgement, minimising but not excluding the risk of transmission of diseases. Once dead, ticks will often drop off the animal, but any remaining ticks may be removed with a gentle pull. Fleas from pets often infest the animal's basket, bedding and regular resting areas such as carpets and soft furnishings which should be treated, in case of massive infestation and at the beginning of the control measures, with a suitable insecticide and vacuumed regularly. When used as part of a strategy for the treatment of Flea Allergy Dermatitis, monthly applications to the allergic patient and to other dogs in the household are recommended. For optimal control of flea infestation in multi-pet household, all dogs and cats in the household should be treated with a suitable insecticide. **Special precautions for use in animals** : Animals should be weighed accurately prior to treatment. Avoid contact with the animal's eyes. In the case of accidental eye contact, immediately and thoroughly flush the eyes with water. It is important to make sure that the product is applied to an area where the animal cannot lick it off and to make sure that animals do not lick each other following treatment. Do not apply the product on wounds or damaged skin. **User Warnings** : This product can cause mucous membrane and eye irritation. Therefore, contact between the product and the mouth or eyes should be avoided. In the case of accidental eye contact, immediately and thoroughly flush the eyes with water. If eye irritation persists seek medical advice and show the package leaflet or the label to the physician. Do not smoke, drink or eat during application. Avoid contents coming into contact with the fingers. If this occurs, wash hands with soap and water. Wash hands after use. Animals or operators with a known hypersensitivity to fipronil or excipients should avoid contact with the veterinary medicinal product. Treated animals should not be handled until the application site is dry, and children should not be allowed to play with treated animals until the application site is dry. It is therefore recommended that animals are not treated during the day, but should be treated during the early evening, and that recently treated animals should not be allowed to sleep with owners, especially children. **Other precautions** : Fipronil may adversely affect aquatic organisms. Dogs should not be allowed to swim in water courses for 2 days after application. The product may have adverse effects on painted, varnished or other household surfaces or furnishings. **Use during pregnancy and lactation** : Laboratory studies using fipronil have not shown any evidence of teratogenic or embryotoxic effect. Studies have not been carried out with this product in pregnant and lactating bitches. Use in pregnancy and lactation only in accordance with professional veterinary advice and a benefit/risk assessment.

■ **SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY**

Dispose of any unused product and empty containers in accordance with guidance from your local waste regulation authority. Fipronil may adversely affect aquatic organisms. Do not contaminate ponds, waterways or ditches with product or empty container.

Summary

- Levels of neonicotinoids and fipronil resulting from authorised uses, frequently exceed lowest observed adverse effect concentrations for a wide range of non-target species and may have negative biological and ecological impacts.
- This statement does not reflect the exclusive use of veterinary medicines.
 - Exposure pathways need to be quantified
- Benefit / risk implications
 - Needs to factor in high benefit

Future considerations

- Other formulation types
- Safety concerns removal of collars etc.
- Consideration at a European level re companion animal risk assessments; revision to VICH?
 - Is exposure significant?
- VMD and other regulatory bodies – investigating a proposal for exposure pathways to be elucidated

Thanks for listening, any questions

