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Updated Summary on Use and Safety of Flea and Tick Preventives for Animals

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Abstract

Objective: Although the development of novel, potent flea and tick preventives began more than 20 years ago, with collars, spot-on topical, and tablets/chews, adverse events associated with their use have recently escalated since these reactions report were reviewed. Adverse events are believed to be grossly underreported, and 3 Class Action lawsuits have been filed in North America.

Materials and methods: The present report updates the previously published Jake Survey conducted in 2018 and published in 2020, to include US Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) adverse events. Along with European Medicines Agency (EMA) data through spring 2021.

Conclusion: Updated results from the USA and European Union indicate a notable increase in the number of particularly serious adverse events reported for the flea and tick preventives including seizures, behavioural aggression, and death. The actual number of adverse incidents is likely much higher than those reported to regulatory agencies.

Keywords: Preventives; Isooxazoline; Parasiticides; Environmental protection agency

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Introduction

Unlike the Food and Drug Administration (FDA) which regulates parasiticides, such as the isooxazoline compounds, the Environmental Protection Agency (EPA) regulates pesticides like the imidacloprid+flumethrin collar. This difference in regulatory authority in the USA has caused confusion among veterinarians and companion animal owners. In contrast, the European Medicines Agency (EMA) regulates all these categories of products [1-3].

Current Class Action lawsuits include one in Quebec and a second in New Jersey involving fluralaner (Bravecto®) and related compounds, due to the incidence of serious AR (Adverse Reactions) including death, that have a duration of treatment lasting from one to 3 months. A third Class Action lawsuit was filed in March 2021 against the imidacloprid+flumethrin product (Seresto Collar®). The collar was introduced in 2012, and is touted to last for 8 months.

The present manuscript provides updated data on these parasite and pesticide products through April 17, 2021, as available from the Food and Drug Administration (FDA), Environmental Protection Agency (EPA) and European Medicines and Agency (EMA) websites and published literature [1-5].

Materials and Methods

The websites for the Food and Drug Administration (FDA) (www.open.fda.gov; API, animal and veterinary endpoints), Environmental Protection Agency (EPA) (www.epa.gov, pesticides, incident-report), and European Medicines and Agency (EMA) (www.ema.europa.eu, pharmacovigilance, incident report) were searched for adverse events reported through April, 2021. These drugs were introduced to the commercial veterinary market from as early as 1996 (ivermectin; HeartGard®, Ivomec®) and to as recently as 2020 for fluralaner+moxidectin (Bravecto Plus®), and for sarolaner+moxidectin+pyrantel+pamoate (Simparica Trio®).

The number of adverse reports was highest for spinosad+milbemycin+oxime (TriFexis®) (200,941) followed by afoxalaner+milbemycin+oxime (NexGard Spectra®) (190,802). The smallest reported number was for the more recently introduced lotilaner (Credelio®, 2018) at 3.302. With regard to the number of reported deaths, the largest number was for sar olaner+moxidectin+pyrantel+pamoate (Simparica Trio®) at 6,717 (approved in 2020), followed closely by spinosad+milbemycin+o xime(TriFexis®) with 6,662 (approved in 2011) and ivermectin+py rantel+pamoate+praziquantel (Iverhart Max®, approved in 2018) at 6,207.

Results

Table 1 lists the Food and Drug Administration (FDA) fluralaner incident reports by species and number of cases. The vast majority of reports involved dogs (86%) with cats accounting for 13%, and 1.5% involving humans.

Parasiticide drug	Species	Number of FDA reports
Fluralaner (Bravecto®)	Dog	38,619
Fluralaner (Bravecto®)	Cat	5,818
Fluralaner (Bravecto®)	Human	674
Fluralaner (Bravecto®)	Wolf	3
Fluralaner (Bravecto®)	Bobcat	2
Fluralaner (Bravecto®)	Tiger	2
Fluralaner (Bravecto®)	Doormouse	1
Fluralaner (Bravecto®)	Fox	1
Total=45,118		

Table 1: FDA (Food and drug administration) records animal and veterinary api endpoints, May 24, 2021.

The official data for all parasiticides used in the U.S. retrieved from the Food and Drug Administration (FDA) through April 17, 2021 included 16 brand name drugs and a total of 1,577,958 Adverse Reactions (AR) with 60,909 deaths **(Table 2)**.

These drugs were introduced to the commercial veterinary market from as early as 1996 (ivermectin; HeartGard®, Ivomec®) and to as recently as 2020 for fluralaner+moxidectin (Bravecto Plus®), and for sarolaner+moxidectin+pyrantel+pamoate (Simparica Trio®).

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It is estimated that only 1% of adverse events are actually reported, and counterfeit flea and tick products have started to flood the commercial pet market [2,3,6].

Table 3 shows The U.S. House Subcommittee on Economic and Consumer Policy called for Elanco Animal Health to "immediately institute a temporary recall of all Seresto® flea and tick collars, following reports that the collars may have killed thousands of pets and may have caused injuries to many more pets as well [6]. Some clinical veterinarians, veterinary internal medicine, dermatology and toxicology specialists continue to defend the safety of this type of product. The reported adverse reactions for Seresto® collars included 11,510 moderate to major in severity, as well as 1,698 deaths **(Table 3)**.

Data (USA) from FDA of reported adverse reactions and deaths after administration of flea, tick and heartworm treatments-updated 4/17/2021				
Brand name	**Active ingredient**	**Introduced to market**	**Adverse reactions**	**Deaths***
Bravecto	fluralaner	2014	43,602	1,533
Bravetco plus	fluralaner+moxidectin	2019-2020	77,459	4,753
Comfortis	spinosad	2012	1,62,354	4.816
Trifexis	spinosad+milbemycin+oxime	2011	2,00,941	6,662
Credelio	lotilaner	2018	3,302	95
Revolution	selamectin	2000	19,552	1,980
Revolution plus	selamectin+sarolaner	2019	31,605	2,346
Nexgard	afoxolaner	2013	36,340	1,086
Nexgard Spectra	afoxolaner+milbemycin+oxime	2014	1,90,802	5,998
Simparica	sarolaner	2016	14,153	432
Simparica trio	sarolaner+moxidectin+pyrantel+pamoate	2020	1,40,646	6,717
Heartgard, Ivomec	ivermectin	1996	94,798	4,103
Heartgard Plus, Triheart	ivermectin+pyrantel+pamoate	2003	1,05,139	5,332
Iverhart Max	ivermectin+pyrantel+pamoate+praziquanel	2018	1,29,815	6,207
Interceptor	milbemyxin+oxime	2013	1,54,190	3,911
Interceptor Plus, Milbemax	milbemyxin+oxime+praziquantel	2,01,02,015	1,72,860	4,938
Totals:			15,77,958	60,909
*This number includes euthanized pets				

Table 2: Summary of Food and Drug Administration (FDA) reported adverse events and deaths through April 2021 (USA only) TriFexis® (spinosad+milbemycin oxime) and Comfortis® (spinosad), both spinosads, generated notable adverse reactions in the Food and Drug Administration (FDA) report of April 17, 2021 in **Table 2**

Pesticide drug	Domestic animal species	Number of EPA reports
Imidacloprid+flumethrin (Seresto Collar®)	Degree of adverse effect	75,000 since 2012
Imidacloprid+flumethrin (Seresto Collar®)	Minor	21, 439
Imidacloprid+flumethrin (Seresto Collar®)	Moderate	7, 743
Imidacloprid+flumethrin (Seresto Collar®)	Major	3,767
Imidacloprid+flumethrin (Seresto Collar®)	Fatality	1, 698
Imidacloprid+flumethrin (Seresto Collar®)	Human	907
Total=40, 087		

Table 3: EPA Office of pesticide programs incident data system, June 16, 2020.

A summary of the reported results obtained from two sources, the Food and Drug Administration (FDA) and Project Jake Survey Is shown in **Table 4**. Serious Adverse Reactions (AR) associated with neurotoxicity included those for death, seizures/convulsions, and shaking/tremors/ataxia.

The cumulative increase in serious Adverse Reactions (AR) for the three isoxazolines reported by the European Medicines Agency (EMA) from 2019 to 2021 is shown in **Table 5.** Results were highest for the European Medicines Agency (EMA) reports, and lowest for the Food and Drug Administration (FDA) reports; those from the Project Jake Survey were displayed to be in between the other two sets of data but closer to those of the European Medicines Agency (EMA). These European Medicines Agency (EMA) cumulative reports through April 2021 paralleled those of our earlier published reporting period through 2017 and 2018 [1].

Table 5 shows the increase in serious neurotoxic Adverse Reactions (AR) for the three isoxazolines reported by the European Medicines Agency (EMA) from 2019 to 2021 is shown in **Table 5**. The overall numbers that involved death and seizures for the January 2013 to April 2021 time frame increased proportionately, as expected if these events had resulted from the pathological effects of the chemical compounds in the products. The cumulative deaths reported to April 2021 ranged from a high of 2,627 (24%) for fluralaner (Bravecto®) to 726 (2.8%) for afoxolaner (NexGard®) and 412 (12.7%) for sarolaner (Simparica®). The cumulative reported seizures ranged from 1,933 (60%) for sarolaner (Simparica®) to 1518 (5.8%) for afoxolaner (NexGard®) **(Table 5)**.

Additionally, an in-depth review has recently been published about the widespread use of fipronil pesticide, which shows neurological effects affecting emotional and cognitive behaviors in mammals, including dogs and cats [5].

FDA serious adverse events reports								
Events reported Jan 2013-Sept 2017	Number and percent of sample population displaying reaction							
	Overall (N=32,374)		Fluralaner (N=16,896)		Afoxolaner (N=14,116)		Afoxolaner (N=14,116)	
Death	801	2.47%	416	2.50%	341	2.40%	44	3.20%
Seizure	1,728	5.34%	468	2.80%	981	6.90%	279	20.50%
Shaking/Tremors/Ataxia	2,223	6.87%	600	3.60%	1,063	7.50%	560	41.10%
Jake survey serious adverse events results								
Events/symptoms aug 2018	Overall (N=1,070)		Fluralaner (N=791)		Afoxolaner (N=235)		Sarolaner (N=44)	
	N	%	N	%	N	%	N	%
Death	147	13.74%%	117	14.79%	28	11.91%	2	4.55%
Seizures/Conclusions	147	13.74%%	117	14.79%	28	11.91%	2	11.14%
Shaking/Tremors/Ataxia	493	43.2%%	271	34.3%%	178	75.7%%	13	29.6%%

Table 4: Summary comparison of serious adverse events for fda and project Jake survey.

EMA adverse event data increase for fluralaner, afoxolaner and sarolaner								
EMA serious adverse events results								
Events reported Jan 2013-Jan	Percent of sample population displaying reaction							
	Overall (N=32,991)		2.40% 341 Fluralaner (N=10,172)		Afoxolaner (N=20,902)		Sarolaner (N=1,917)	
Death	3,186	9.66%	2,408	23.70%	528	2.53%	250	13.04%
Seizure	4,002	12.13%	1,860	18.30%	1,087	46.69%	1,055	55.10%
EMA serious adverse events results								
Events reported Jan 2013-Apr 2021	Percent of sample population displaying reaction							
	Overall (N=40669)		Fluralaner (N=11097)		Afoxolaner (N=26330)		Sarolaner (N=3242)	
Death	3,765	9.26%	2,627	23.67%	726	2.76%	412	12.71%
Seizure	5,753	14.15%	2,302	20.74%	1,518	5.77%	1,933	59.62%
FDA serious adverse events reports								

Table 5: EMA (European Medicines Agency) adverse event data increases for fluralaner, afoxolaner and sarolaner.

Discussion

The results shown here document that the adverse events reported in the U.S. and European Union are continuing to increase as these products and new 'spot-ons', collars, topicals, and internal flea and tick parasiticides and pesticides continue to be used.

When examining the Food and Drug Administration (FDA), Adverse Reactions (AR) reports for active ingredients of a common class, the data in **Table 2** show that spinosad containing treatments (Comfortis® and Trifexis®) resulted in a combined 363,295 AR reports with 11,478 deaths, followed by afoxolaner treatments (Nexgard® and Nexgard Spectra®) with 227,142 reports containing 7,084 deaths; sarolaner treatments (Simparica® and Simparica Trio®) with 154,799 reports and 7,149 deaths; and fluralaner formulations (Bravecto® and Bravecto Plus®) with 121,061 reports and 6,286 deaths. It is also noted that recently Food and Drug Administration (FDA) approved (2020) multi-compound formulations (Bravecto Plus® and Simparica Trio®) had markedly increased numbers of Adverse Reactions (AR) reports and deaths in a short period of post-marketing reporting when compared to the original product formulations. Since 2018, lotilaner (Credelio®)

has had 3,302 reports with 95 deaths: noticeably fewer incident reports than for 2020 approved Bravecto Plus® or Simparica Trio®. Similarly, apparent 'improved' product formulation releases for Interceptor Plus® (2015), Iverhart Max® (2018), and Revolution Plus® (2019) have all shown moderate to marked increases in adverse reaction reports and deaths when compared to their respective earlier formulations.

It is also noteworthy that of the 45,118 Food and Drug Administration (FDA) Adverse Reactions (AR) reports by species in **Table 1**, 674 were for humans, whereas the Environmental Protection Agency (EPA) Office of Pesticide Programs Incident Data System **Table 3** showed 907 human AR (Adverse Reactions) reports; indicative of human exposure/toxicity at a level that is significant enough to warrant submission of a human event record for a pet product.

What is particularly disconcerting, especially now that additional adverse events are required to be listed on the product labels and inserts, is the fact that treating veterinarians continue to prescribe them despite these new warnings and the moderate to marked increases in Adverse Reactions (AR) reports [7-14].

Pet caregivers are rarely informed about these side effects and so may only find out about them from pet magazines, news media reports, and on-line accounts [12,13]. Further backlash against revealing these adverse effects have come not only from industry employed veterinarians and scientists but also from private practitioners, and specialist veterinarians. Some veterinarians working for companies manufacturing these products have asserted that they regularly use them on their own pets.

The first author of this report frequently encounters dog owning clients that are referred for holistic alternative care of pets exhibiting the classical adverse effects seen from using these parasiticides or pesticides. Prescribed by their local veterinary clinics. This misleading situation parallels that of local veterinarians and veterinary cardiologists that still tell clients to avoid grain-free pet foods as they cause Dilated Cardiomyopathy (DCM) shown in **Table 6**. The more recent peer-reviewed published data to refute these original large pet food producer claims has either been ignored or discounted, or proponents are unaware of them [15-17].

Events reported jan 2013-Sept 2017	Number and percent of sample population displaying reaction							
	Overall (N=32,374)		Fluralaner (N=16,896)		Afoxolaner (N=14,116)		Sarolaner (N=1,361)	
Death	801	2.47%	416	2.50%	341	2.40%	44	3.20%
Seizure	1,728	5.34%	468	2.80%	981	6.90%	279	20.50%
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	N	%	N	%	N	%	N	%
Death	147	13.74%%	117	14.79%	28	11.91%	2	4.55%
Seizures/Convulsions	147	13.74%%	117	14.79%	28	11.91%	2	11.14%
Shaking/Tremors/Ataxia	493	43.2%%	271	34.3%%	178	75.7%%	13	29.6%%

Table 6: Number and percenft off sampfle popuflafion dfispflayfing reacfion.

The co-authors of the present report also have encountered denials or ignorance of this latest information. The question remains about the motivation or reasons for professional veterinary colleagues and their teaching institutions to fail to relay or be aware of these updates.

Conclusion

Updated results from the USA and European Union indicate a noteworthy increase in the number of reported adverse events from the flea and tick preventives and collars beyond what was originally on the product labels, including seizures, behavioural aggression, and death. The actual number of adverse incidents is likely much higher than is reported. The veterinary profession has been less than forthcoming in informing their clients about these potential serious side effects.

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