White Paper – Pesticides and the Veterinary Professional: Outcomes of EPA's Seresto® Review and the Criticality of Adverse Event Reporting

Note to the reader: This document expands on the Veterinary Practice News article "Tips for Reporting Adverse Events" (February 2025), highlighting the critical role of adverse event reporting in the Seresto review and includes a summary of the EPA's evaluation outcomes.

On July 13, 2023, the Environmental Protection Agency (EPA) completed their comprehensive, multi-year review of the Seresto collar, confirming the product's continued registration. Pursuant to the review, Elanco and EPA developed a stewardship program that Elanco is implementing as a leader in the collar category. One key element of the stewardship program is implementation of communications to ensure the US veterinary community is informed of the risks and benefits associated with the use of pesticides in pet products, including Seresto, and the importance of reporting adverse events (AEs).

The following discussion has been composed in support of veterinary outreach with the intent of providing important information regarding the safety profile of pesticides, including Seresto, and the criticality of AE reporting.

Pesticides in animal health products

The EPA defines a pesticide as "Any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest."[1] While pesticides are used in many ways in public health, they play a pivotal role in animal health – particularly in flea and tick products. In the US, pesticidal products are under the jurisdiction of the EPA whereas animal drugs are regulated by the Food and Drug Administration's Center for Veterinary Medicine (FDA-CVM).

Pesticidal active ingredients, such as imidacloprid, fipronil, permethrin, and flumethrin, can be found in most over-the-counter flea and tick treatments and preventatives. Imidacloprid and fipronil have been used in products for years to control flea infestations, while flumethrin and permethrin effectively kill and repel ticks.

Parasite preventatives that include pesticides undergo rigorous safety and efficacy testing and must demonstrate their meaningful impact on parasite burden to merit a label claim. This process is similar in many ways to antiparasitic drug products. Like drugs, all pesticidal products are monitored following registration to ensure ongoing safety and efficacy (i.e., pharmaco-vigilance). Pharmacovigilance practices are critically dependent on reports from pet owners and veterinary professionals.

Product complaints or AE reporting

The American Veterinary Medical Association (AVMA) describes an AE as any observation in animals or humans, whether or not the cause of the event is known, that is unfavorable and unintended, and that occurs after any use (as indicated on the label or any extralabel use) of a product, including events related to a suspected lack of expected effectiveness.[2] The International Cooperation on Harmonisation of Technical Requirements for Registration of

Veterinary Medicinal Products (VICH) similarly defines an AE as any observation in animals, whether considered to be product related or not, that is unfavorable and unintended – occurring after any exposure to, or use of a marketed product.[3] The AVMA states, "adverse events are rare and the majority of them are minor, but some can be life-threatening."[4] As noted, AEs can involve on- and off-label uses of a product. In addition to untoward health effects for the treated animal, AEs may include events related to a suspected lack of expected efficacy as well as noxious reactions in humans after being exposed to a product or events related to the environment or residues in food. Remember that the event may or may not be caused by the product and that correlation in timing of product administration does not always equal causality when it comes to a potential AE.

Adverse event reporting plays a critical role in monitoring product safety, improving treatment protocols and informing future research. Once the animal's medical needs are met, the AE should be reported by the attending veterinarian or knowledgeable clinic staff regardless of how minor the AE may seem. The best place to find details on how to report an AE is the product label or packaging which will provide contact information for the manufacturer. Note that manufacturers are required to report AEs to the oversight agency.

Why AE reporting matters

The commitment of veterinarians to AE reporting is crucial to increasing knowledge within the animal health and scientific community. As the AVMA reminds us, veterinarians reporting AEs provide regulatory authorities and manufacturers with reliable and critical information that is used to monitor and evaluate the safety and efficacy of products and devices used in the field.[5] The quality of the information provided by the veterinary team is extremely important in creating accurate AE reports that provide high-quality, foundational data for use in monitoring product safety.

Individual AE information becomes part of a larger data set which can be analyzed and reviewed to monitor for trends and safety signals over a product's life cycle. When an AE is reported, it allows government agencies and manufacturers to investigate and determine if the involved product's label or directions for use should be adjusted. These insights are invaluable, as they contribute to the veterinary community's shared knowledge and help us continually improve industry standards and practices – benefiting veterinarians, their clients, and their patients.

AE reporting and the Seresto review

The Seresto evaluation underscores the critical importance of AE reports submitted by veterinary professionals. These reports formed a cornerstone of the EPA's in-depth scientific review, which spanned AE data from the product's initial registration in 2012 through 2020. The EPA's comprehensive scientific review leveraged these reports alongside other data sources, including companion animal safety studies, toxicological data, and active ingredient release rates. By comparing Seresto to similar products and consulting with the FDA, the EPA conducted a thorough analysis detailed in their AE review document.[6] This case highlights the essential role of AE reports in monitoring pet product safety.

Outcomes of the Seresto review

The most frequently reported clinical sign for Seresto in dogs was pruritus (itchy skin) and was reported in 54% of the reported incident cases (of 49,000 cases). This was followed by lethargy and anorexia, each of which was reported in approximately 10% of cases. For cats, application site hair change was the most frequently reported sign (32% of 16,000 cases) followed by application site lesions and pruritus, each of which was reported in approximately 25% of cases. More severe clinical signs (for example, convulsions) were reported much less frequently and appeared to be similar across the three Elanco products that were compared.[7]

Seresto's labels now include a Post Approval Experience (PAE) section as relevant to dogs and cats specifically which lists reported AEs (see Table 1) and a recommendation for the pet owner to remove the collar and consult their veterinarian if these symptoms occur.

Table 1 Post-Approval Experience (adverse events listed in decreasing order of reporting frequency)

Dogs	Pruritus (itchy skin), vomiting, lethargy, behavioral disorders, application site reactions (dermatitis, inflammation, eczema, alopecia or lesions), anorexia, hyperactivity, muscle tremor, vocalization, convulsion, ataxia (problems with balance and coordination).
Cats	Application site reactions (hair change, lesions, pruritus, erythema, inflammation, hemorrhage, burns, self-trauma, ulcers), behavioral disorders, lethargy, anorexia, vomiting, alopecia, hyperactivity, skin disorders, vocalization, skin lesion, hypersalivation.

Reporting AEs: a linear process

To understand the importance of reporting AEs, let's review the steps encompassing an AE report. These steps show a linear process from start to finish, outlining what happens when a veterinary professional reports an AE.

1. A suspected AE is observed by the veterinary team and/or reported to the team by a pet owner.
2. A member of the veterinary team reports the AE according to the product label.
    a. The label clearly lists contact information for the manufacturer or animal health company. The following information will be requested at a minimum:
        · Reporter identification
        · Animal details (species as a minimum)
        · Product identification
        · AE details
    b. In addition, the reporting of information regarding the patient's concomitant medical conditions or products administered and results of any diagnostic testing is recommended as it allows the animal health company/manufacturer to more completely evaluate the report and determine causes of the potential AE.
3. The animal health company/manufacturer records the AE and reports to the appropriate regulatory authority as required by legislation.

4. The animal health company/manufacturer evaluates data for trends and potential safety signals.

Conclusion

Adverse event reporting is fundamental to effective pharmacovigilance. Without this information, manufacturers and government agencies cannot make informed decisions regarding product safety in the field. Collective responsibility and collaboration between veterinary teams, pet owners, the regulatory agencies, and manufacturers are crucial for high-quality AE reporting, enabling data-driven decisions and positive change.

In the case of Seresto, AE reporting by veterinary professionals provided a critical lens through which to evaluate product safety, allowing thorough review and appropriate closure of the investigation.

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[1] What is a Pesticide? Last updated February 13, 2025. https://www.epa.gov/minimum-risk-pesticides/what-pesticide

[2] Adverse Event Reporting. 2024. American Veterinary Medical Association. Accessed 9/10/24. www.avma.org/resources-tools/avma-policies/adverse-event-reporting#:~:text=An%20adverse%20event%20is%20any

[3] Veterinary Medicines Directorate. 2001. "Glossary." GOV.UK. Accessed 9/10/24.

[4] Reporting Adverse Events. 2024. American Veterinary Medical Association, Accessed 9/10/24. www.avma.org/resources-tools/animal-health-and-welfare/animal-health/reporting-adverse-events.

[5] Reporting Adverse Events. 2024. American Veterinary Medical Association, Accessed 9/10/24. www.avma.org/resources-tools/animal-health-and-welfare/animal-health/reporting-adverse-events.

[6] Canine and Feline Adverse Event Review for the Seresto Collar (EPA Reg No. 11556-155)

[7] EPA's Memorandum in Support of the Regulatory Decision for PNR 1427 (Seresto Pet Collar, EPA Reg. No. 11556-155)