נספח 1

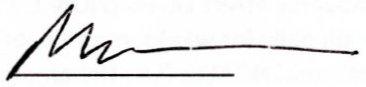
**Expert Opinion of Dr. Robert H. Poppenga, DVM, PhD, DABVT**

I, the undersigned, Dr. Robert H. Poppenga, have been requested by the Respondents in Class Action 50744-01-23 Yampolsky *et al*. v. Elanco Animal Health GMBH *et al*., conducted in the Central District Court in Israel, to provide my professional opinion regarding the claims raised in general in the Amended motion to certify the class action and in particular in the expert opinion of Professor Eyal Klement on behalf of the Applicants, which primarily, and in general terms, alleges the potential harm of Seresto collars to dogs and cats.

I provide this opinion in lieu of testimony in court, and I hereby declare that I understand, concerning the provisions of criminal law regarding false testimony under oath in court, this opinion signed by me is considered as testimony under oath that I provided in court.

Furthermore, I hereby confirm that I have no dependency on the opinion or the respondents, except for the fact that I receive fee for this opinion. Additionally, I hereby confirm that my fee is not contingent upon the results of the opinion or the legal proceeding.

March 14, 2024
Date


Signature

**Introduction and Executive Summary**

**"There is no evidence from the study that the active ingredients of Seresto® caused any adverse events".** This is merely one example of the conclusion I reach after having evaluated many studies [for a full discussion see pages 13-29] that show that the allegations made in the class action have no merits whatsoever.

In the course of an Amended Motion to Certify the filing as Class Action brought in Israel, the plaintiffs tried to challenge the safety of the Seresto® collar. In support of their claim, they provided an expert opinion submitted by Professor Eyal Klement (the "Klement Report", Appendix 2 to the Amended Motion to Certify the filing as Class Action)).

I have been asked to provide my expert opinion with regard to the safety of the Seresto® collar for dogs and cats and to respond to the Klement Report and its conclusion. **As I describe in my opinion, the Seresto® collars are safe. They received all necessary approvals from the regulatory authorities and all data, studies, and research made in this field prove it.** Unlike the Klement Report, which does not contain any proof against the use of the Seresto® collars, I believe that those collars can be safely used. Many regulatory authorities agree.

I would state at the beginning of my opinion that Seresto® collars, which contain 4.5% flumethrin and 10% imidacloprid, are designed to protect pets from fleas and ticks for 8 months. The active ingredients of the collar are incorporated into a polymer matrix which are then released in low concentrations over the life-span of the product. Flumethrin is the active ingredient (AI) responsible for the efficacy of the product against ticks and imidacloprid is the AI responsible for the efficacy of the product against fleas.

The safety of the collar has been questioned based upon reported adverse effects following its application to pets despite extensive safety and efficacy studies that indicate the collar is safe when used as directed. I have reviewed the toxicological data on the active ingredients in the Seresto® collar, the potential synergy between the active ingredients, clinical and field studies in which the collar has been evaluated, and regulatory materials concerning the Seresto® collar and adverse events reported in connection with its use. I conclude that:

- Clinical and field studies on the Seresto® collar indicate that it is safe for use as intended. Specifically, over 2,300 animals have been treated with a Seresto® collar in clinical or field studies conducted in multiple countries spanning three continents. As I discuss below, those studies did not observe any adverse events that could be attributed to the active ingredients in the Seresto® collar. All that was observed was local skin irritation and hair loss, especially in animals that were wearing multiple collars simultaneously in order to achieve an exaggerated dose, and which are related to the mechanical act of wearing a collar.
- Based on toxicological data, the Seresto® collar delivers sufficiently low doses of the active ingredients that one would not expect to see adverse effects. Specifically, based on calculations I explain below, Seresto® collars release a maximum of 0.61 mg/kg/day of flumethrin and 10.79 mg/kg/day of imidacloprid. Not only do those figures fall below the dermal No Observed Adverse Effect Levels (NOAEL; i.e., the amount of a chemical that can be applied to an animal's skin daily for weeks, months, or even years without causing adverse effects), but they fall below the oral NOAELs (i.e., the amount an animal can eat daily over a period of weeks, months, or even years without causing adverse effects). Thus, even if an animal were to consume 100% of the flumethrin and imidacloprid released by the collar each day, it would not be expected to experience adverse effects relating to either active ingredient.
- It has been alleged that Health Canada's Pest Management Regulatory Agency (PMRA) evaluated 251 reports of pet death with a Seresto® collar and concluded that 33% of them were linked to the collar. PMRA has not released the details of that analysis to my knowledge, but a recent report by the United States Environmental Protection Agency (USEPA) discloses that PMRA only concluded 3% of the deaths were "probably" related to the collar, with 30% merely "possibly" related. Moreover, USEPA evaluated the same 251 death reports and concluded, as recently reported by USEPA in July 2023, that deaths categorized as "probably" related to the collar were caused by mechanical strangulation or trauma (a risk of all collars) and not by the active ingredients in Seresto®. Indeed, USEPA wrote that: "In incident reports where details were provided, **EPA did not identify a strong correlation between collar use and death, often due to other factors impacting the animal, such as an existing medical condition. All of the reported death cases that were found to be probably or definitely related to Seresto product use were associated with mechanical strangulation or trauma. In addition, the rate of deaths reported was similar between Seresto and the other pet products reviewed.**" This is important, because USEPA's overarching findings regarding deaths were similar to PMRA's. Thus, it is plausible that the deaths that PMRA linked to the collar were likewise those that were caused by mechanical issues and not by the active ingredients.
- My conclusion, as I describe in the opinion below, is that the Seresto® collar is safe when used as intended.

The Klement Report offers Dr. Klement's opinion on three questions. I respond at length below, but my overarching response to his opinions on those three questions is follows:

- Question posed: "Is there a causal link between the usage of animals' pest extermination collars (that carry the commercial name "Seresto," inter alia) and the reports for unexpected side effects and deaths among animals (and even humans) that are related to the collars"?

    - My response: There is no evidence sufficient to support a causal link between the application of Seresto® collars to animals as intended and any significant side effects other than local skin and hair effects relating to the mechanical act of wearing the collar. The doses of active ingredients delivered by Seresto® are below the threshold at which any adverse effects would be anticipated, and clinical and field studies on the collars have established the collar's safety.

- Question posed: "Do the existing studies, including Bayer's clinical and pre-clinical studies rule out the causal link between the above reports and the unexpected side effects and deaths"?

    - My response: This question not only assumes that there are unexpected side effects and deaths that are potentially attributable to Seresto® collars but also ignores the nature of the studies themselves. It is not possible to prove with 100% certainty that a chemical or other product causes no as-yet-unobserved side effects. However, in light of the extensive toxicological testing and clinical studies that were performed both before and after Seresto® was submitted to the regulatory authorities, my opinion is that the studies are adequate and collectively show that the application of Seresto® collars is unlikely to cause any adverse effects other than local skin and hair effects relating to the mechanical act of wearing the collar.

- Question posed: "Whether the findings regarding side effects and deaths should have been in epidemiological point of view evidence to require the defendants' reference and public warning, and if so from what date"?

    - My response: As there is no evidence sufficient to support a causal link between the application of Seresto® collars to animals as intended and any significant side effects other than local skin and hair effects relating to the mechanical act of wearing the collar, which are already addressed appropriately in the product labels (both in the United States labels I cite below and in those found in Appendix 6 to the Amended Motion to Certify the filing as Class Action, each of which discloses hair loss and mild skin reactions as well as the possibility of skin inflammation, eczema, or a wound), I do not believe the "findings regarding side effects and deaths" to which this question refers were caused by Seresto® collars. Thus, per my review, I do not believe any references or warnings must be added beyond what the product's labeling already provides.

I discuss certain limitations and critiques of Dr. Klement's opinions throughout this report, but in general my disagreement with him is as follows:

- Dr. Klement appears to assume, based on his interpretation of the conclusion of a still-undisclosed analysis of selected death reports by PMRA, and a staff report by the United States House Committee on Oversight and Reform, Subcommittee on Economic and Consumer Policy (which Dr. Klement appears to have misinterpreted as an official report by the United States Congress) that largely draws on that same conclusion, that there is a causal link between the death reports in question and Seresto® collars. As I explain at length below, though, the PMRA

and staff report conclusions are not only obscure but are called into serious question by USEPA's recent review. To be more specific, USEPA's analysis suggests that PMRA did not ascribe any deaths to the active ingredients in the Seresto® collar. Dr. Klement errs by assuming otherwise.

- Moreover, Dr. Klement does not appear to engage meaningfully with the toxicological data or the clinical studies on Seresto®, except to cite a few published studies (which did not disclose any concerning signs, as he seems to agree and as I explain below) and then argue that the sample sizes were too low to ensure that very rare adverse events were all observed. However, his failure to meaningfully address the toxicological data in light of the doses delivered by Seresto® undermines the nature of his analysis. One might observe, for example, that no study has been performed on a large enough sample of trees to categorically exclude the possibility that some small fraction of them is capable of higher thought. That observation, however, is neither useful nor enlightening given all else we know about trees – for example, that they do not have brains. The lack of a study proving that trees do not think at a high level is not itself reason to perform such a study, nor is it evidence that trees are in fact sentient. In the same way, the toxicological data I discuss below indicates that one would not expect to see any adverse effects at the dosages of flumethrin and imidacloprid delivered by Seresto®. Thus, Dr. Klement's observation that the sample size of studies to date is insufficient to rule out the possibility of some adverse effect that occurs at a rate of 0.03-0.05% is not itself reason to conduct larger studies, let alone to assume it is possible that rare adverse effects exist but have thus far gone unappreciated. This is mere speculation.

- Mathematically, Dr. Klement's example is that a sample size of 6,000 would be required in order to have a 95% chance of observing a death if the death rate is 0.03-0.05%. First, it is notable that there would still remain a 5% chance of failing to observe such a rare event even in a 6,000-animal sample size; indeed, the equation that Dr. Klement uses to calculate those figures ([Sample size] = Ln(1-[level of certainty])/Ln(1-[rate of event])) shows that it is impossible to reach 100% certainty of a product's absolute safety through clinical studies alone, regardless how large they are. It is therefore not realistic to call for 100% certainty. Moreover, using the same equation, a study with a sample size of 1,386 would have a 50% chance of observing an event that occurs at a rate of 0.05%. In the case of Seresto®, over 2,300 Seresto®-treated animals were observed in clinical or field studies; even ignoring the toxicological data, the studies alone make it less than 50% likely that a side effect that occurs at a rate of at least 0.05% - five in 10,000 – went unobserved. In fact, the current sample size in studies alone yields a 95% chance of having observed an adverse effect that occurs at a rate of at least 0.13% - 1.3 in 1,000.

- In short, Dr. Klement assumes – rather than demonstrates – a causal link between unspecified side effects and Seresto® collars. His assumption appears to be based on an interpretation of PMRA's still-undisclosed analysis, which interpretation appears incorrect in light of USEPA's recent analysis. Then, Dr. Klement reviews just a subset of the available evidence – none of which affirmatively *suggests* a causal link – and claims it is insufficient to *reject* the causal link he has assumed.

**USEPA Assessment – 2023**

In July 2023, USEPA [U.S. Environmental Protection Agency – the regulatory authority for Seresto®] announced the findings of its review of the Seresto® collar's safety (USEPA, 2023a [EPA-HQ-OPP-2021-0409-0287], available at https://www.regulations.gov/document/EPA-HQ-OPP-2021-0409-0287). The

review was prompted by a petition from the Center for Biological Diversity to cancel the product's US registration (i.e., remove it from the market) in April 2021, which was itself prompted by the > 75,000 adverse event reports that had been then-recently disclosed. USEPA denied the petition. The summary of USEPA's review of the reports of pet deaths (p. 2) is particularly illuminating:

> In incident reports where details were provided, EPA did not identify a strong correlation between collar use and death, often due to other factors impacting the animal, such as an existing medical condition. All of the reported death cases that were found to be probably or definitely related to Seresto product use were associated with mechanical strangulation or trauma. In addition, the rate of deaths reported was similar between Seresto and the other pet products reviewed.

USEPA reviewed 1,096 canine death cases and 381 feline death cases (USEPA, 2023b [EPA-HQ-OPP-2021-0625-0015], available at https://www.regulations.gov/document/EPA-HQ-OPP-2021-0625-0015, p. 35). Only four canine cases and nine feline cases were found to be probably or definitely related to the collar, and all 13 of those cases (0.88% of total reported deaths) "were associated with mechanical strangulation or trauma caused by the collar, rather than the active ingredient contained in the collar." Although it is unfortunate that such deaths occurred at all, this is a risk that cannot be completely eliminated for pet collars and does not reflect at all on the safety of Seresto®'s chemical composition.

USEPA's analysis sheds interesting light on PMRA's evaluation. According to the staff report by the United States House Committee on Oversight and Reform, Subcommittee on Economic and Consumer Policy (Appendix 9 to the Amended Motion to Certify the Filing as Class Action), the transcript of the Subcommittee hearing (Appendix 15), and Dr. Klement's summary, PMRA and USEPA both evaluated 251 pet deaths and found that 33-45% of them "were probably or possibly caused by the collar." I am not aware of PMRA identifying the 251 pet deaths at issue or disclosing its analysis; notably, USEPA was provided with a "draft (incomplete) plausibility analysis provided by PMRA [but] never received a final copy of this document," though USEPA did at least have "incident data and discussions with PMRA" (USEPA, 2023b [EPA-HQ-OPP-2021-0625-0015], p. 83). However, the USEPA report (USEPA, 2023b [EPA-HQ-OPP-2021-0625-0015], p. 85) establishes that PMRA only deemed 3% of deaths "probable" (versus USEPA's 2%) and the remainder merely "possible." **This is notable because USEPA reviewed all reported pet deaths (including the 251 deaths) in its most recent analysis and found no deaths to be even "probably" related to the active ingredients.** The 2% that USEPA deemed "probably" related in the 251-pet data set must therefore have involved mechanical deaths. Though the details of PMRA's review remain unclear, the similarity in the results of PMRA's and USEPA analyses as reported by USEPA suggests that the 3% of deaths PMRA deemed "probably" related to the collar likewise might not have involved the active ingredients.

USEPA's analysis is also at odds with the apparent implication of the testimony of Karen McCormack as cited in Dr. Klement's report (see also Ms. McCormack's testimony at Appendix 15 to the Amended Motion to Certify the Filing as Class Action, pp. 12-13). USEPA did not receive 2,300 reports of pet death "from the use of a pet collar called Seresto." **On the contrary, it received zero reports of pet death it could deem even "probably" related to the active ingredients.**

USEPA also evaluated causation in a subset of non-death cases in which neurological signs were reported. As noted above, given the mode of action of Seresto®'s active ingredients, one would expect neurological signs to be the most plausible adverse effect attributable to the active ingredients.

However, as USEPA agreed following its re-review of the toxicological data (USEPA, 2023b [EPA-HQ-OPP-2021-0625-0015], p. 21), measured plasma concentrations in collar-bearing dogs and expected release rates from the collar are both so low that no adverse effects would be expected to occur. Nevertheless, USEPA did evaluate some neurological signs as "probably" caused by the Seresto® collar (USEPA, 2023b [EPA-HQ-OPP-2021-0625-0015], p. 38). It is notable that all of the "probably" related neurological signs occurred in dogs, whereas one would expect to see more signs in cats due to increased oral exposure through self-grooming. As I discuss in more detail below, dogs have a relatively high background rate of neurologic conditions (including a per-year seizure incidence of 0.82%, per Erlen *et al*. (2018)); it is not surprising that convulsions/epileptic seizures were the most common adverse events in the subset of neurological signs USEPA investigated. Indeed, based on the report from Erlen *et al*., one would expect about 22 dogs per million (i.e., 0.82%/365 = 0.0022%, or 22 per 1,000,000) to experience a seizure on any given day even if a Seresto® collar has not been applied. That remains the case on days 5-6 after a Seresto® collar is applied, which as I discuss below is when the active ingredients reach peak concentration; for every million dogs that wear a Seresto® collar, random chance alone would predict that about 44 will experience a seizure during those two days of peak exposure but is caused by wholly unrelated factors. Per the American Veterinary Medical Association (https://www.avma.org/news/epa-confirms-registration-safety-seresto-collar), over 41 million Seresto collars have been sold in the United States; even if only half of those were dog collars, one would expect about 108,240 seizures to occur in dogs that were wearing a Seresto® collar solely due to the background rate of seizure (20.5 million dog collars x 240 days of wear per collar x 22 seizures per million dog-days). Of those, about 3,150 seizures would be expected to occur in the first week after collar application, including about 900 during the two days of peak exposure, again due solely to chance alone and unrelated to the collar. Timing alone therefore cannot support an inference of causation, as timing that might be "suspicious" if observed in a small sample size becomes expected when dealing with such large numbers of collars sold. Even time-based trends in reporting data should be viewed skeptically, as one would expect an owner or veterinarian to be more likely to assume a link between the seizure and the collar if the collar had been recently applied when the seizure occurred rather than months earlier (by which time the collar would no longer be top of mind for the owner or veterinarian).

It does not appear that USEPA has released a detailed analysis of any of the neurological signs it deemed probably related to the collar, so it is difficult to comment on its findings. In addition, it is unclear whether signs were reported only by the pet owner or were observed by a veterinarian. Neurological signs reported by pet owners are likely to be quite subjective and not adequately discerning to help with an evaluation of causality. In my opinion a clinical sign of "disorientation" is so vague as to not be very useful. In addition, there did not appear to be an evaluation of causality based upon the number of signs reported for an individual animal, and in those cases where multiple clinical signs were reported, the sequence of onset of clinical signs. For example, it would be expected that muscle tremors would precede seizures given the known mechanism of action of the active ingredients. The causality scores appear to apply to only one neurologic sign even if multiple signs were exhibited by an animal. For dogs, there were 480 reported neurologic signs reviewed for 369 animals. So, some individuals exhibited more than one sign.

Moreover, as I discuss in detail below, Seresto®'s active ingredients have a toxicologic profile that suggests a dosage too low to cause adverse effects. USEPA agreed, concluding that plasma/serum studies "suggest[] systemic exposure to the active ingredients from collar wear are lower than those levels where clinical signs may be observed," particularly in dogs, where there were additional plasma concentration studies available that further suggested the dosage was too low to cause adverse effects (USEPA, 2023b [EPA-HQ-OPP-2021-0625-0015], p. 44-45). This, together with the fact that some small

*percentage* of animals wearing Seresto® collars (but not necessarily a small overall *number*, given the large number of collars sold) are expected to experience adverse events while the collar is in place solely due to the background rate of those events, makes it unclear what sort of presentation could yield a rating of "probable" under the scoring rubric USEPA used (USEPA, 2023b [EPA-HQ-OPP-2021-0625-0015], p. 92-94). A score of +3 is necessary to yield a rating of "probable," but a positive score should be impossible to achieve in the categories of Previous Experience with Drug, Alternative Etiologic Condition, and Evidence of Overdose based on the toxicological and clinical studies outlined above. One would therefore need scores of 0 in all three of those categories *and* positive scores in the remaining three categories (Timing of Event, Dechallenge, and Rechallenge) merely to score an adverse event as "probably" related to a Seresto® collar. In the case of seizure, this would only be the case if a collar were applied, and a seizure occurred about a week thereafter, and then the collar was removed for a time, and the animal suffered no seizures, and then the collar was reapplied, and the animal then experienced another seizure. But even in such a case, an animal with a history of seizure, individual characteristics suggestive of predisposition for seizure, or other explanations would score a -1 on Alternative Etiologic Condition and could not be rated more highly than "possible." This is not impossible, but I am skeptical that it explains all seven of the dogs that USEPA deemed to have experienced seizures "probably" related to Seresto®.

**Moreover, as I discuss below, one must first show that a treatment is capable of causing an effect before opining that it has done so in a particular instance. I see no evidence that Seresto® is capable of causing neurological signs in dogs or cats when used as intended. The toxicological testing provides evidence that Seresto® delivers too low a dose of the active ingredients to cause adverse effects during normal wear, and the clinical studies and field studies do not provide any evidence to the contrary. The adverse event reporting data at most show an association, and not causation, between Seresto® and the adverse events complained of; even if USEPA has concluded that some neurological adverse events were "probably" caused by the collar, I have difficulty seeing how that conclusion was based on anything other than timing considerations (which cannot, by themselves, prove causation). And even under those circumstances, USEPA allowed Seresto® to remain on the market and did not prohibit the sale of the collars.**

**Biographical Sketch**

I have nearly 35 years of experience in veterinary toxicology and food safety as a result of working in several veterinary diagnostic laboratories. I routinely conduct forensic investigations into a variety of potential accidental and malicious animal poisonings involving numerous animal species, often involving an assessment of causation. I have supervised and directed state-of-the-art veterinary diagnostic toxicology sections with a broad array of analytical capabilities and diversity of case submissions.

I received my DVM and PhD degrees from the University of Illinois in 1978 and 1987, respectively. During my PhD studies I was also a staff veterinarian for the National Animal Poison Control Center at the College of Veterinary Medicine (the center subsequently became the ASPCA Animal Poison Control Center). Since receiving my PhD and residency training in veterinary toxicology, I have held faculty positions at Michigan State University, University of Pennsylvania and University of California at Davis (UCD) veterinary schools.

I have taught professional, graduate and undergraduate students using a variety of teaching formats including case- and problem-based learning modalities. I also train residents in veterinary toxicology as part of my duties with the California Animal Health and Food Safety Laboratory System (CAHFS). I

initiated a bi-weekly collaborative case-based discussion group with veterinary toxicologists and residents at U. of Kentucky, Iowa State University, and Kansas State University. While at the University of Pennsylvania I led the effort to develop a computer aided learning module on poisonous plants. I currently serve on the Admissions and Graduate Student Advisory Committees of the Forensic Science Graduate Group and the Graduate Student Advisory Committee of the Pharmacology and Toxicology Graduate Group at UCD.

In my current role of Toxicology Section Head at CAHFS, I supervise 11 FTE analytical chemists and staff with over 100 years of combined experience across all analytical systems. Our laboratory has a full array of analytical capabilities including LC/MS (and HRMS), GC/MS, ICP/MS, LC/ICP/MS, and ELISA analytical platforms. We have a unique capability to approach chemical contamination incidents from a variety of clinical and analytical perspectives. My research interests include diagnostic veterinary toxicology, wildlife toxicology, and development of biomarkers for chemical exposure. I am an author/co-author on more than 160 peer-reviewed publications and numerous book chapters.

Since 2004, the CAHFS Toxicology Section has received support through the Food Emergency Response Network (FERN) and Veterinary Laboratory Investigation and Response Network (VetLIRN) Chemistry Programs and I have been the PI on those cooperative agreements.

I am active in several professional organizations including the American Association of Veterinary Laboratory Diagnosticians (Regional Executive Board Member, Journal of Veterinary Diagnostic Investigation Editorial Board, and member of the Committee on Toxicology and Environmental Issues), American Board of Veterinary Toxicology (Secretary/Treasurer, Vice President, President, Examination Committee Chair, and Education Committee), and the American Veterinary Medical Association (Committee on Environmental Issues).

During the previous five years, I have testified as an expert at trial and by deposition in the case of *Raza v. Spain and Randall*, SC 122344 Superior Court in the State of California, County of Los Angeles, Central District, 2016/2017. In January 2019, I testified by deposition in the case of *Loeb v. Champion Petfoods*, No. 18-cv-494-JPS in the Eastern District of Wisconsin. In May 2019 and August 2019, I also testified by deposition in the case of *Reitman v. Champion Petfoods*, No. 2:18-CV-01736-DOC in the Central District of California. In October 2019, I testified by deposition in the case of *Zeiger v. Wellpet LLC,* No. 4:17-CV-04056 WHO in the Northern District of California. In November and December 2020, I testified by deposition in the case of *Song v. Champion Petfoods*, No. 18-cv-03205-PJS-KMM in the District of Minnesota. In March 2021, I testified by deposition in the case of *Zarinebaf et al. v. Champion Petfoods*, No. 1:18-cv-06951 in the Northern District of Illinois, Eastern Division. This was followed by testimony in a related Daubert Hearing in September 2021. In July, 2023, I provided an expert opinion in *Corbett et al. v. Cargill, Incorporated et al.*, W.D. Ky. Court File No. 22-cv-00281-CRS.

The materials and documents that I examined and used throughout the preparation of my opinion are listed at the end of my opinion.

**The Seresto® Collar**

The Seresto® collar comprises a polymer matrix containing 4.5% flumethrin and 10% imidacloprid by weight. The collar comes in two sizes. The large collar weighs 45 g and is labeled for dogs weighing over 18 lbs/8 kg, whereas the small collar weighs 12.5 g and is labeled for smaller dogs (i.e., up to 18 lbs/8 kg) and cats (Lunchick, 2010). The small collar is not to be used on puppies less than seven weeks of age

(https://www.elancolabels.com/seresto-small-dog) or on kittens less than 10 weeks of age (https://www.elancolabels.com/us/seresto-cat) (see also Israeli product labels, Appendix 6 to the Amended Motion to Certify the Filing as Class Action).

The Seresto® collar has been shown from the very early stages of its marketing to be very effective against fleas and ticks, not only in an extensive suite of clinical tests comparing Seresto® to no-treatment control (see Cyton Biosciences, 2018 for a summary of such studies) but also in a number of randomized trials comparing Seresto® to other treatments and finding Seresto® to be superior with regard to efficacy (e.g., Stanneck *et al*., 2012a; Horak *et al*., 2012). I do not delve deeply into efficacy in this report, inasmuch as Dr. Klement agrees that "Seresto collars have been proven to be effective in preventing infection (sic) with external parasites and effective in preventing infection with disease agents transmitted by these parasites." (Klement Report). I would add that the DEFRA report on which he relies (DEFRA, 2019) likewise concluded that Seresto® is effective, and that "[t]he overall risk/benefit analysis is in favour of granting a marketing authorisation." Thus, Dr. Klement is disagreeing with authorities who have reviewed more information than he has and concluded that the collar is safe. I reserve the right to supplement this report if the efficacy of the Seresto® collar is called into question.

When evaluating the safety of the Seresto® collar, several points must be kept in mind. First, there is some degree of risk inherent to all collars, including those that do not bear any medications or other chemically active ingredients. All pet collars are capable of mechanically rubbing against an animal's neck and causing local skin irritation, hair loss/thinning, and other local adverse effects. Those effects can increase the risk of infection. All pet collars are also capable of causing strangulation and limb or mouth injuries (https://www.petmd.com/dog/care/5-ways-collars-can-harm-your-dog). These risks are unavoidable for pets that wear collars. One cannot merely assume that such adverse effects are related to the design or chemical composition of the Seresto® collar, rather than to the mere act of wearing a collar.

Second, all adverse events have some rate of background occurrence. For example, in one large study in the UK encompassing 455,553 dogs, seizures were observed in 0.82% of the population during the one-year study duration alone (Erlen *et al*., 2018). The observed rate varied based on breed (some breeds had a more than three-fold higher risk than the average), sex (males faced a 47% higher risk), and weight (animals over 40 kg were 24% more likely to experience seizures than animals less than 10 kg). That study reported a per-year seizure rate, meaning that lifetime risk is substantially higher than 1%. This has two implications. First, one cannot simply assume that a seizure (or any other adverse event) in an animal wearing a Seresto® collar was caused by the collar because some percentage of the animals would experience that same adverse event even if they had never worn the collar. Indeed, applying the Erlen analysis as I discuss above, some 22 dogs out of every million are expected to experience a seizure any given day of the year. For every million dogs who receive a Seresto® collar, one would expect to see around 22 of them have a seizure the day the collar is placed based on chance alone. Another 22 or so would be expected to have a seizure the following day, and so forth, all without any relation at all to the collar. Given the number of Seresto® collars that have been sold, this highlights the need to evaluate each adverse event individually against the background risk the animal faced had the collar not been used. Second, there are individual risk factors that significantly impact the background risk an animal faces. Those individual risks must be accounted for when assessing the cause of an adverse event in a particular animal. Thus, even if Seresto® were proven to be capable of causing a particular adverse effect in some small percentage of animals, it would be scientifically unsound to assume causation in any individual animal without evaluating that animal's individual characteristics, antemortem or postmortem clinical and diagnostic assessment.

Third, there are several fundamental toxicologic concepts that need to be considered for determining whether exposure to a chemical causes an adverse effect. One foundational pillar in toxicology is the concept of dose-response. This means that as the exposure dose in mg (or dosage in mg/kg body weight) increases one can expect an enhanced response. The response could be a beneficial response (e.g., from a drug acting therapeutically) or an adverse response (causing an unwanted reaction). Chemicals only cause an effect when administered in doses that exceed a certain "threshold" dose or dosage. That is, even where a chemical has been proven capable of causing an effect, there exists a dosage below which the chemical will not cause that effect. Risk assessments need to consider toxic thresholds, but also exposures below a toxic threshold for which no adverse effect is noted. Thus, measures such as the No Observed Adverse Effect Level (NOAEL), No Observed Effect Level (NOEL) or Lowest Observed Effect Level (LOAEL) are important for risk assessments and adverse effect (AE) evaluations. These parameters are then used to compare to known exposure levels to judge the likelihood of an unwanted reaction occurring.

Another foundational pillar is whether an adverse effect following a chemical exposure makes sense from the known mechanism(s) of action of the chemical. The mechanisms of action of the AI in Seresto collars are well known and affect the nervous system. If observed clinical signs are not related to the nervous system, then it is unlikely that the signs would be due to flumethrin and or imidacloprid exposure. In other words, the clinical signs need to be plausible based upon knowledge about how the insecticides work.

Considering the aforementioned toxicologic concepts, there are two aspects to establishing a causal link between a treatment and an effect. First, one must show that the treatment is capable of causing the effect (i.e., "general causation"). Only then can one attempt to show that the treatment caused the effect in a particular instance (i.e., "specific causation"). With respect to veterinary products like Seresto®, toxicological testing is an important element of establishing or ruling out general causation. As I discuss in further detail below, toxicological testing intentionally exposes study animals to specified doses of a chemical through various means in order to establish certain thresholds below which adverse effects do not occur (i.e, No Observable Adverse Effect Level or NOAEL). For a product that delivers a dose of a treatment that has been shown to be too low to cause the adverse effect in question, "general causation" has not been established. As I explain below, my analysis of the toxicological testing on the active ingredients in Seresto® suggests that they are highly unlikely to cause any adverse effects at the doses delivered. It is inappropriate to ignore the toxicological evidence of Seresto®'s safety when discussing whether an adverse event such as a seizure or pet death has been caused by Seresto®. One must first explain how Seresto® could deliver a dose above the NOAEL and cause an adverse event notwithstanding the toxicological evidence to the contrary. Such an inquiry is necessarily individualized to each pet exhibiting symptoms alleged to be associated with a Seresto® collar.

Moreover, one must distinguish between the concepts of association and causation. Association merely means that a treatment and an effect co-occur at a higher rate than would be expected based on chance alone. But not all associations are causal. For example, the divorce rate in the state of Maine correlates well with the per capita consumption of margarine (for this and numerous other examples, see e.g. http://www.tylervigen.com/spurious-correlations). However, there is clearly no causal relationship despite the high degree of association; margarine consumption does not cause divorce, nor does divorce cause margarine consumption. Likewise, assume that animals that have received Seresto® collars at some point in their life are shown to be more likely than others to have had a tick or flea infestation at some point in their life as well. One who has not investigated the relationship might assume from this

association that Seresto® is causing tick or flea infestation; however, that assumption becomes untenable when considering the evidence that Seresto® is quite effective at killing and repelling ticks and fleas. Thus, when faced with a demonstrated association between a treatment and an effect, one must examine the relationship more deeply before inferring that the treatment causes the effect. In the case of Seresto® collars, I do not believe that there is even a demonstrated association between any observed adverse effects and the collar's active ingredients. Because association is a prerequisite for causation, this is further evidence in support of my conclusion that no adverse effects can be attributed to the active ingredients in Seresto® collars.

In my opinion, these principles explain why my assessment of the safety of Seresto® differs from that of both PMRA and Dr. Klement. PMRA's analysis of the adverse event reports remains confidential and therefore unexplained, so it is unclear how or even whether it evaluated background rates or individual circumstances before assessing causation in individual instances. It is also unclear who performed the assessments, or what their qualifications were. As I note elsewhere, though, USEPA has reviewed the same 251 death reports that PMRA reviewed and concluded that none of those deaths were even "probably" related to the active ingredients in Seresto®. USEPA's analysis supports the safety and benefit of the collars. Dr. Klement likewise gives the above-discussed concepts little attention in his report, which appears to merely assume Seresto® is capable of causing the adverse events he discusses rather than actually evaluating causation.

**Pyrethrins/Pyrethroids**

One of the active ingredients in the Seresto® collar, flumethrin, belongs to a class of compounds called pyrethrins/pyrethroids. Pyrethrins (pyrethrin I and II, jasmolin I and II, and cinerin I and II) are insecticidal compounds derived from the flowers of *Tanacetum cinerariifolium*. The use of pyrethrins dates back to approximately 400 BC in Persia. Pyrethroids are synthetic analogs of pyrethrins and were developed primarily to improve environmental stability and target organism toxicity (Holynska-Iwan and Szewczyk-Golec, 2020). Pyrethrin and pyrethroid insecticides are effective against a variety of pests and have been used on livestock and companion animals, around homes and gardens, and for public health and crop protection. Because of their mammalian safety profiles, pyrethrins/pyrethroids have replaced more toxic organophosphorus and carbamate insecticides for many uses.

Pyrethroids are classified as first or second generation. First generation pyrethroids are esters of chrysanthemic acid and an alcohol with furan ring and terminal side chain moieties. Second generation pyrethroids have 3-phenoxybenzyl alcohol derivatives in the alcohol moiety and a dichlorovinyl or dibromovinyl substitute and aromatic rings replacing terminal sidechain moieties. The addition of an α-cyano group to the 3-phenoxylbenzyl alcohol in the second generation pyrethroids increases insecticidal potency.

The toxicity of various pyrethroids has high variability with acute oral toxicity for mammals of 100 to 2000 mg/kg body weight (Dalefield, 2017) or greater.

Table 1: Dermal and oral $LD_{50}$s for various pyrethrins/pyrethroids

| | Type | Dermal $LD_{50}$ (mg/kg bw)[1] | Rat oral $LD_{50}$ (mg/kg bw)[1] |
|---|---|---|---|
| Pyrethrin | I | >2000[2] | 900 |
| Allethrin | I | 2500 (rat) | 680 |

| | | | |
|---|---|---|---|
| Tetramethrin | I | >5000 (rat) | 4640 |
| Resmethrin | I | >2000 (rabbit) | 100 |
| Permethrin | II | >2000 (rabbit) | 2000 |
| Cypermethrin | II | 1600 (rats), >2000 (rabbits) | 500 |
| Deltamethrin | II | 700 to >2940 (rats) | 31 |
| Fenvalerate | II | 5000 (rat) | 450 |
| Fluvalinate | II | >20,000 (rats and rabbits) | 1000 |
| Flumethrin | II | 1436 | 175 |

[1]The provided $LD_{50}$s are for general comparative purposes and derived from a variety of sources. $LD_{50}$s can vary depending on factors such as vehicle used (see flumethrin below), rodent strain, and sex. The $LD_{50}$ of flumethrin was taken from the Seresto® collar MSDS.

[2] Values that are > means that those were the highest dosages used to determine acute dermal toxicity and that the true $LD_{50}$s could be substantially higher.

Pyrethroids are lipid soluble and, to varying degrees, can be systemically absorbed following dermal, oral, or pulmonary exposure. Systemic bioavailability following dermal exposure is approximately 1 to 2% and in the range of 40% to 60% following ingestion (Ensley, 2018a). Pyrethroids are excreted by first-order kinetics via the urine and feces as a mix of parent compound and metabolites (Ensley, 2018). The half-lives of pyrethroids in plasma are relatively short (i.e., hours) (Thiphom *et al*., 2014; Ensley, 2018a).

Pyrethroids act on voltage-gated sodium channels. Binding of pyrethroids to the α subunit of the channel causes its permanent opening and prevents it from closing. As a result of the influx of sodium ions into nerve cells sustained depolarization occurs. This causes the excitation of nerve cells and maintains them in a stable hyperexcitable state. The duration of effect is longer for type II pyrethroids than for type I pyrethroids.

The decreased sensitivity of mammals to this class of insecticides compared to insects is due to several factors:

- stronger binding to sodium channels at lower ambient temperatures (25°C for insects vs. 37°C for mammals).
- mammalian sodium channels are ~ 1000 times less sensitive than insect sodium channels.
- mammalian sodium channels recover more quickly following depolarization than insect sodium channels.
- mammals generally metabolize pyrethrins/pyrethroids more efficiently than insects.

Neurotoxicity from pyrethroids, when observed, is considered to be due to acute effects and not chronic or cumulative effects (Ensley, 2018a). In dogs, cats and livestock, the clinical signs associated with intoxication are similar for both type I and type II pyrethroids. Clinical signs include salivation, vomiting, hyperexcitability, tremors, seizures, dyspnea, weakness, prostration and death. Type II intoxication can be associated with choreoathetosis (a movement disorder characterized by involuntary twitching or writhing).

The majority of reports of pyrethroid intoxication in the peer-reviewed veterinary medical literature involve cats. The pyrethroid most often associated with intoxication is permethrin which is a type I pyrethroid. It is generally thought that cats are more sensitive to the effects of pyrethroids because most pyrethroids are metabolized through a pathway requiring glucuronidation, a process in which cats are deficient (Stanneck *et al.*, 2012a). Thus products containing pyrethroids such as permethrin or deltamethrin are not used on cats. However, flumethrin is safe to use on cats because it is excreted directly as flumethric acid through a metabolic pathway that does not involve glucuronidation (Stanneck *et al.*, 2012a).

**Flumethrin**

Flumethrin is a type II synthetic pyrethroid. It is an ectoparasiticide that is used in a variety of animal products including dips, pour-ons, strips, and collars (EMEA 1998). Like other pyrethroids, it acts by binding and stabilizing voltage-gated sodium channels in the open state, thus maintaining nerve cells in a depolarized and thus hyperexcitable state.

*Dermal No Observed Adverse Effect Level (NOAEL):* As mentioned earlier, this is the amount that can be applied to an animal's skin daily over the course of weeks, months, or even years without causing adverse effects. A dermal NOAEL of 10 mg/kg body weight was determined in a 90-day study in Wistar rats (Schladt, 2010). In contrast, Seresto® delivers an average of only 0.47 mg/day for the small collar and 1.67 mg/day for the large collar (Lunchick, 2010). Thus, the maximum dermal dose for the smallest animal for which the large collar is recommended (i.e., 8 kg or larger, as the large collar is labeled for animals 8 kg or larger) would be 0.21 mg/kg/day (i.e., 1.67 mg/day divided by 8 kg), or 2.1% of the NOAEL. The small collar does not carry a weight restriction to my knowledge but is labeled only for felines 10 weeks of age or older and canines 7 weeks of age or older. Animals meeting those age restrictions can be expected to exceed 0.774 kg (i.e., the weight of the smallest 10-week kitten included in the studies described below), with most weighing significantly more. Using that conservative weight estimate, though, the maximum dermal dose for a small animal would be 0.61 mg/kg/day (i.e., 0.47 mg/day from the small collar divided by 0.774 kg), or 6.1% of the NOAEL. Thus, the maximum dermal flumethrin exposure from Seresto® (0.61 mg/kg/day) is more than an order of magnitude below the dermal NOAEL. I note as well that mean exposures measured in actual animals across over 20 studies never reached this theoretical level and were generally below 0.20 mg/kg/day, topping out at 0.44 mg/kg/day (Stanneck, 2010). Notably, although several individual animals in those studies were calculated to have received higher doses, each instance of an animal receiving more than 0.61 mg/kg/day involved either (1) a calculation based on just two days of exposure (which would not constitute a chronic dose so as to implicate the 90-day NOAEL), with subsequent measurements on the same animal showing sharply reduced doses, and/or (2) animals that were wearing at least three Seresto® collars concurrently as part of the studies I describe below (Stanneck, 2010). Because the amount of flumethrin delivered on a chronic basis is not sufficient to cause adverse effects, it is also true that the amount of flumethrin delivered is not sufficient to cause acute effects. **One would not expect even *ten times* the amount of flumethrin delivered to an animal merely from wearing a Seresto® collar to cause adverse effects.**

- Multiple studies assessing the release rate in the first 30 days disagree as to whether flumethrin is released more rapidly in the first 30 days than in the remaining months of the Seresto® collar's use (Lunchick, 2010). However, even the highest average flumethrin release rates

measured in the early wear period (1.41 mg/day for the small collar and 2.92 mg/day for the large collar) correlate to maximum daily exposures of 1.82 mg/kg/day and 0.36 mg/kg/day for the small and large collars, respectively, and are still five-fold below the dermal NOAEL. They would not be expected to cause adverse effects even if those rates persisted indefinitely, rather than slowing to the rates described above. Notably, the highest exposure measured in the > 20 studies summarized by Stanneck (2010) for an individual animal that was not wearing multiple collars was 0.71 mg/kg/day as measured at Day 2 (a measurement on the same animal at day 56 showed exposure at just 0.10 mg/kg/day). Thus, even the highest daily dosage measured in an animal wearing a single collar was more than ten-fold below the dermal NOAEL and did not persist.

*Dietary No Observed Adverse Effect Level (NOAEL)*: As mentioned earlier, this is the amount that an animal can eat daily over a period of weeks, months, or even years without causing adverse effects. A 13-week feeding study in Beagle dogs established a dietary No Observed Effect Level (NOEL; essentially equivalent to NOAEL) of 25 mg/kg feed equivalent to a dosage of 0.88 mg/kg body weight per day. (EMEA 1998). In a 15-week feeding study in Wistar rats, the oral NOAEL for flumethrin was determined to be 10 ppm feed, equivalent to 0.7 mg/kg/day for males and 0.8 mg/kg/day for females (Bomann, 1995). Ninety-day neurotoxicity testing in Wistar rats determined an oral NOAEL of 1.0 mg/kg/day for both sexes (Gilmore, 2008). As calculated above, the amount of flumethrin delivered to an animal's skin by the Seresto® collar is not expected to exceed 0.21 mg/kg/day for large animals or 0.61 mg/kg/day for small animals. These numbers are both below the dietary NOAEL even for the most conservative of the studies discussed above, meaning that adverse effects would not be expected even in the unlikely event that an animal were to consume 100% of the flumethrin delivered by the collar each day (e.g., during grooming). Again, because the amount of flumethrin delivered on a chronic basis is not sufficient to cause adverse effects, it is also true that the amount of flumethrin delivered is not sufficient to cause acute effects. **Thus, one would not expect the amount of flumethrin released from the Seresto® collar during normal wear to cause adverse effects even if the animal were to consume all of the flumethrin each day (e.g., during grooming)**.

- Dr. Klement concedes in his report that a flumethrin dosage of 0.88 mg/kg/day (i.e., the oral dose described above) does not cause side effects in dogs. He does not, however, compare this NOEL to the amount of flumethrin that the Seresto® collar is capable of delivering. The above analysis shows that Seresto® does not deliver a dose sufficient to cause concern even if one uses a more conservative NOEL than Dr. Klement concedes. As such, I can say that the Klement report does not support the claim that the amount of flumethrin to which animals are exposed by Seresto® collars is capable of causing adverse effects.

- One might argue that systemic exposure could be somewhat higher if an animal were to consume a collar in whole or in part. It is difficult to estimate the likely range of exposure in that scenario, as I am not aware of any testing on the rate of release of the active ingredients from the Seresto® collar when ingested. Nor would I expect there to be such testing, as the collar is not intended for consumption. However, I note that occasional reports have been made of pets eating a collar on occasion, but serious adverse effects have been rare. (E.g., National Pet Poison Helpline Affirms Safety of Seresto Flea and Tick Collar Use, May 26, 2012. PR Newswire,

https://www.prnewswire.com/news-releases/national-pet-poison-helpline-affirms-safety-of-seresto-flea-and-tick-collar-use-301299291.html).

Flumethrin is not carcinogenic, mutagenic, teratogenic nor a reproductive toxicant (DEFRA, 2019; USEPA, 2023 [EPA-HQ-OPP-2021-0625-0015], available at https://www.regulations.gov/document/EPA-HQ-OPP-2021-0625-0015). Flumethrin has been well tolerated by target species (e.g., dogs and cats) when administered topically at recommended dosage rates.

In sum, based on the toxicological testing, I conclude that the amount of flumethrin released from the Seresto® collar is unlikely to be sufficient to cause adverse events in dogs or cats wearing the collar. Of further note, I observe that all humans are larger than the smallest animal that can wear a small collar, and all humans over 8 kg/18 lbs are larger than the smallest animal that can wear a large collar. Therefore, for the same reasons that I believe the flumethrin exposure is too low to cause adverse events in animals wearing the Seresto® collar, I conclude that the exposure is also too low to cause adverse events in humans.

**Neonicotinoids**

The second active ingredient in the Seresto® collar, imidacloprid, belongs to a class of compounds called neonicotinoids. Neonicotinoids are a class of insecticides that are widely used in veterinary medicine and plant agriculture. The neonicotinoid insecticides include imidacloprid, acetamiprid, dinotefuran, thiamethoxam, and clothianidin. Imidacloprid is the most widely used insecticide globally.

Neonicotinoids act on post-synaptic nicotinic receptors which, in insects, are located within the peripheral nervous system. Imidacloprid acts on at least 3 different subtypes of nicotinic receptors in cockroaches. Mammals also have multiple subtypes of nicotinic receptors formed from different combinations of nine α, four β, and γ, δ, ε forms. Neonicotinoids have much lower activity in vertebrates compared to insects due to different binding properties to their nicotinic receptors (Ensley, 2018b).

Table 2: Dermal and oral $LD_{50}$s for neonicotinoid insecticides.

| Insecticide | Dermal $LD_{50}$ (mg/kg bw) | Rat oral $LD_{50}$ (mg/kg bw)[1] |
|---|---|---|
| Imidacloprid | >5000[2] (rats) | 450 mg/kg |
| Acetamiprid | >2000 (rats) | 200 to 220 mg.kg |
| Dinotefuran | >2000 (rats | 2450 mg/kg |
| Thiamethoxam | >2000 (rats) | 1563 mg/kg |
| Clothianidin | >2000 (rats) | 523 to 1216 |
| Nitenpyram | >2000 (rats) | 1575 to 1680 mg/kg |

[1]The provided $LD_{50}$s are for general comparative purposes and were derived from a variety of sources. $LD_{50}$s can vary depending on factors such as vehicle used, rodent strain, and sex.
[2] Values that are > means that those were the highest dosages used to determine acute dermal toxicity and that the true $LD_{50}$s could be substantially higher.

**Imidacloprid**

Imidacloprid, a chloronicotinyl nitroquanadine compound, was introduced in the U.S. in 1994 as a veterinary flea control treatment, structural pest and crop insecticide, and a seed treatment. According to the National Pesticide Information Center (NPIC) over 400 products are for sale in the U.S. that contain imidacloprid (either alone or combined with other active ingredients). Formulations include liquids, dusts, granules, packets that dissolve in water and various flea product formulations such as collars or spot-ons (NPIC Imidacloprid General Fact Sheet, http://npic.orst.edu/factsheets/imidagen.html).

Imidacloprid affects the nervous system of a target insect by competitively inhibiting nicotinic acetylcholine receptors. Binding to postsynaptic nicotinic receptors prevents the neurotransmitter acetylcholine from binding and transmitting information. Impairment of normal nerve function results in death of the target insect.

When administered orally, imidacloprid is rapidly absorbed, metabolized primarily in the liver and excreted predominately in urine (Ensley, 2018b). Absorption and distribution of imidacloprid in rats occurs within 1 h following oral administration. In mammals, imidacloprid is not distributed to the central nervous system (CNS), fatty tissues or bone. Thus, the blood-brain barrier in mammals prevents distribution into the CNS; this is true for neonicotinoids more generally. There are two routes of imidacloprid metabolism in mammals (Ensley, 2018b). The first route of metabolism involves oxidative cleavage of imidacloprid to imidazolidine and 6-chloronicotinic acid. The imidazolidine moiety is excreted in the urine. The 6-chloronicotinic acid is further degraded by glutathione conjugation to a derivative of mercapturic acid, then to methyl mercaptonicotinic acid. The mercaptonicotinic acid is then conjugated with glycine to form a hippuric acid conjugate that is excreted. A second route of metabolism involves hydroxylation of the imidazolidine ring followed by elimination of water and formation of an unsaturated metabolite. In rats, more than 90% of a dose of imidacloprid is eliminated within 24 h (Ensley, 2018b). Imidacloprid does not accumulate in the body, and it is not carcinogenic, mutagenic, teratogenic nor a reproductive toxicant. Imidacloprid has a high margin of safety due to the high insecticidal nicotinic receptor specificity (Ensley, 2018b).

*Dermal No Observed Adverse Effect Level (NOAEL or NOEL)*: Again, this is the amount that can be applied to an animal's skin daily over the course of weeks, months, or even years without causing adverse effects. Dermal toxicity of imidacloprid is low, with an acute dermal No Observed Effect Level (NOEL) of 5000 mg/kg body weight in rats (DEFRA, 2019). Fifteen-day dermal toxicity studies on rabbits have shown no effect at 1000 mg/kg of imidacloprid (NPIC Imidacloprid Technical Fact Sheet, http://npic.orst.edu/factsheets/archive/imidacloprid.html). The daily rate of release of imidacloprid from the Seresto® collar is 8.35 mg/day for the small collar and 22.7 mg/day for the large collar during the first 30 days and decreases thereafter (Lunchick, 2010). Thus, the maximum dermal dosage for an animal large enough to wear the large collar (i.e., 8 kg or larger, as the large collar is labeled for animals 8 kg or larger) would be 2.84 mg/kg/day (i.e., 22.7 mg/day divided by 8 kg), or 0.28% of the lowest NOEL. The small collar does not carry a weight restriction to my knowledge but is labeled only for felines 10 weeks of age or older and canines 7 weeks of age or older. Animals meeting those age restrictions can be expected to exceed 0.774 kg as described above, with most weighing significantly more. Using that conservative weight estimate, though, the maximum dermal dosage for a small animal would be 10.79 mg/kg/day (i.e., 8.35 mg/day from the small collar divided by 0.774 kg), or 1.08% of the

lowest NOEL. I note as well that mean exposures measured in animals across over 20 studies never exceeded 7.36 mg/kg/day, with the highest exposure measured in any individual animal being 7.85 mg/kg/day and the vast majority of measured exposures being considerably lower (Stanneck, 2010). Thus, dermal imidacloprid exposure from Seresto® is about two orders of magnitude below the dermal NOEL. Because the amount of imidacloprid delivered on a chronic basis is not sufficient to cause adverse effects, it is also true that the amount of imidacloprid delivered is not sufficient to cause acute effects. **One would not expect even *100 times* the amount of imidacloprid delivered to an animal merely from wearing a Seresto® collar to cause adverse effects.**

- Dr. Klement cites a study from the "University of Murray" in which it was shown that imidacloprid penetrates an animal's skin and enters the systemic circulation. First, the possibility of dermal penetration is already accounted for in the dermal NOEL. If a chemical does not cause adverse effects at a certain dosage when applied to the skin, that inherently means that there is insufficient dermal penetration to cause systemic adverse effects as well.

- Second, I assume Dr. Klement is referring to the study by Craig *et al.* (2005) from researchers at Murray State University. In that study, an imidacloprid spot-on product was applied to dogs. The researchers then evaluated concentrations of imidacloprid on gloves used to pet the treated dogs and in the blood of treated dogs. The maximum concentrations on the gloves reached 254 parts per million on average, compared with just 54 parts per billion in the blood samples. That is, the concentration of imidacloprid on a glove that had stroked the dog was nearly 5,000 times greater than the concentration in the dog's blood. This shows that, although some small portion of the imidacloprid is making its way into the systemic circulation, the vast majority of the imidacloprid remains on the animal's hair and skin. Moreover, as the authors note, "[a]t no time during the study period did the dogs show any signs of toxicity." Therefore, in my opinion, the Klement report does not prove that the dose of imidacloprid released by the Seresto® collar poses a significant health risk.

*Dietary No Observed Adverse Effect Level (NOAEL)*: Again, this is the amount that an animal can eat daily over a period of weeks, months, or even years without causing adverse effects. The oral NOAEL for imidacloprid has been estimated at 14 mg/kg/day based on three-month feeding studies in rats (NPIC Imidacloprid Technical Fact Sheet, http://npic.orst.edu/factsheets/archive/imidacloprid.html). Studies in dogs have produced similar results. A 52-week study in dogs at oral doses up to 72 mg/kg/day of imidacloprid did not produce tremors. The no observed effect level for this chronic oral exposure dog study was 15 mg/kg (Ensley, 2018b). As calculated above, the amount of imidacloprid delivered to an animal's skin by the Seresto® collar is not expected to exceed 2.84 mg/kg/day for large animals and 10.79 mg/kg/day for small animals. These numbers are both below the dietary NOAEL, meaning that adverse effects would not be expected even if an animal were to absorb 100% of the imidacloprid delivered by the collar each day (e.g., via the skin or via ingestion from grooming). Again, because the amount of imidacloprid delivered on a chronic basis is not sufficient to cause adverse effects, it is also true that the amount of imidacloprid delivered is not sufficient to cause acute effects. **Thus, one would not expect the amount of imidacloprid released from the Seresto® collar during normal wear to cause adverse effects even if the animal were to consume some or all of the imidacloprid each day (e.g., dermal absorption and/or during grooming)**.

- Dr. Klement does not address the toxicology of imidacloprid in his report, let alone compare the NOAEL to the amount of imidacloprid that the Seresto® collar is capable of delivering. He does, however, concede that neonicotinoids (including imidacloprid) are significantly less toxic in mammals than in insects. In my opinion, this supports the safety of Seresto® rather than that the collar poses a risk.

In sum, based on the toxicological testing, I conclude that the amount of imidacloprid released from the Seresto® collar is unlikely to be sufficient to cause adverse events in dogs or cats wearing the collar. Of further note, I observe that all humans are larger than the smallest animal that can wear a small collar, and all humans over 8 kg/18 lbs are larger than the smallest animal that can wear a large collar. Therefore, for the same reasons that I believe the imidacloprid exposure is too low to cause adverse events in animals wearing the Seresto® collar, I conclude that the exposure is also too low to cause adverse events in humans.

**Flumethrin + Imidacloprid**

The combination of flumethrin and imidacloprid as found in the Seresto® collar has been shown to be particularly efficacious for controlling fleas and ticks on dogs and cats for an extended period of time when used as directed. Bayer conducted numerous laboratory and field efficacy and safety studies in adult dogs and cats, puppies, and kittens as required by USEPA prior to product approval. I review a number of these studies below. In all, 530 cats and 527 dogs had been treated with Seresto® in studies conducted prior to marketing of the collar in the United States. Over 1,300 more have been treated in subsequent studies. (Cyton Biosciences, 2018). Each animal who received a Seresto® collar in these studies provides evidence as to the safety of flumethrin and imidacloprid in combination.

When using chemical combinations there is always the potential for interactions that can be additive or synergistic. An additive effect occurs when the combined responses of two chemicals is equal to the sum of the responses to each chemical given alone (1 + 1 = 2). A synergistic effect occurs when the combined responses of two chemicals are much greater than the sum of the response to each chemical when given alone (1 + 1 = 5). In the case of flumethrin being used simultaneously with imidacloprid, a primary toxicologic concern would be for an additive or synergistic effect to occur due to their combined mechanisms of action on nervous cells. Both insecticides stimulate nerve cells, albeit at different sites (i.e., sodium channels for flumethrin and nicotinic receptors for imidacloprid).

It is possible that imidacloprid and flumethrin could act synergistically in the limited sense of increasing flumethrin's insecticidal activity. Imidacloprid activates nicotinic acetylcholine receptors, which in turn depolarizes the neuronal plasma membrane and causes voltage-gated sodium channels to open. This increases the ability of flumethrin to act by binding to voltage-gated sodium channels in the open state and stabilizing that state. That said, it is likely that any such possible synergistic effect is modest. Imidacloprid's activation of nicotinic acetylcholine receptors is effectively irreversible in insects due to the strength of binding and the inability of acetylcholinesterase to cleave imidacloprid. Thus, the neuronal plasma membrane would be expected to remain depolarized following imidacloprid treatment. This, in turn, would cause a percentage of voltage-gated sodium channels to remain in the open state even in the absence of flumethrin; adding flumethrin would likely increase that percentage to a degree, but the impact of flumethrin would be limited where the dose of imidacloprid is already sufficient by itself to hold open a large percentage of voltage-gated sodium channels. **In sum, the**

**modes of action for imidacloprid and flumethrin suggest that there could be modest synergy as relates specifically to their effect on insect nerve cells. There is, however, no reason to believe this synergistic effect would impact other systems or processes. For example only, one would not expect imidacloprid and flumethrin to act synergistically with respect to carcinogenicity or to cause adverse effects impacting the cardiovascular, gastrointestinal, or endocrine systems.**

Consistent with this reasoning, there is *indirect* evidence for a synergistic effect based upon the ability of the combination to impact insect neuron cells and to kill fleas *in vitro* (Stanneck *et al.*, 2012b). Analysis of spike activity in isolated *Spodoptera frugiperda* neuron cells treated with imidacloprid alone, flumethrin alone, or a combination of imidacloprid and flumethrin revealed that flumethrin alone exerted very little effect (mean of 14 counts per second ("cps") over five runs, relative to a baseline of 3 cps). Imidacloprid alone measured 67.1 cps on average, whereas the combination of imidacloprid and flumethrin measured 91.8 cps. This result is consistent with the above reasoning in that (1) imidacloprid alone (which would be expected to hold open a percentage of voltage-gated sodium channels) had a substantial impact even without flumethrin, and (2) adding flumethrin increased the effect synergistically, but the synergistic effect was minimal. On the other hand, in a series of experiments in which *Ctenocephalides felis* fleas were kept in glass vials coated with either imidacloprid, flumethrin, or a combination of the two, imidacloprid alone had a relatively weak insecticidal activity whereas flumethrin alone was more effective. Although the synergistic effect was relatively modest compared to flumethrin alone, it was more significant compared to imidacloprid alone.

- Dr. Klement acknowledges that the above-described study demonstrated a synergistic effect on the nervous system of **insects**. I agree – that is all that the study demonstrated. But it cannot be extrapolated to assume, for example, a synergistic effect on other systems in any animal, particularly in view of Dr. Klement's apparent agreement with my description of the likely mechanism of synergy given above. Nor can it be extrapolated to assume a synergistic effect in mammals, which as described above, have potentially consequential differences in how they metabolize the compounds and how sensitive the target receptors/channels are to those compounds (see also below). Therefore, the Klement report is insufficient to establish that there is a risk of synergistic effect when using imidacloprid and flumethrin in combination, whether in the Seresto® collar or otherwise, to treat dogs and cats.

**There is toxicological evidence that the synergistic effect exerted on the nervous system of insects does not occur in mammals**. In a study by Andrews (2002), rats were given varying single oral doses of flumethrin alone (2, 3, 5, or 10 mg/kg, three animals per dose), imidacloprid alone (150, 200, 250, or 400 mg/kg, three animals per dose), or one dosage of the combination (5 mg/kg flumethrin plus 150 mg/kg imidacloprid, five animals) via stomach tube. Although the author wrote that the experiment "was deemed to indicate an additive effect" (i.e., still not a synergistic effect), based on my review of the data I do not believe that there was even an additive effect. Clinical signs were observed as follows:

| Clinical Sign | 3 mg/kg Flumethrin Alone | 5 mg/kg Flumethrin Alone | 5 mg/kg Flumethrin plus 150 mg/kg Imidacloprid |
|---|---|---|---|
| Uncoordinated gait | 100% (3/3) | 100% (3/3) | 100% (5/5) |
| Piloerection | 100% (3/3) | 100% (3/3) | 100% (5/5) |
| Labored breathing | 100% (3/3) | 100% (3/3) | 80% (4/5) |

| | | | |
|---|---|---|---|
| Increased salivation | 100% (3/3) | 100% (3/3) | 80% (4/5) |
| Temporary digging movements/cleaning gestures | 100% (3/3) | 100% (3/3) | 40% (2/5) |
| Decreased motility | 100% (3/3) | 100% (3/3) | 20% (1/5) |
| Reactivity decreased | 100% (3/3) | 100% (3/3) | 20% (1/5) |

Thus, the group that received both 5 mg/kg flumethrin and 150 mg/kg imidacloprid in combination showed the same signs that were observed in the 5mg/kg (and 3 mg/kg) flumethrin-only group, but they were observed with equal or *less* frequency in the combination group than in the flumethrin-only group. Moreover, the maximum intensities of the clinical signs for the combination group ranged from 1-2 (similar to the 3 mg/kg flumethrin group, despite that the combination group received a higher dose of flumethrin), whereas all signs in the 5 mg/kg flumethrin-only group were rated an intensity of 2. Though the durations of the signs were expressed as a range that makes comparison somewhat more difficult, I also note that all of the signs in the 5 mg/kg flumethrin-only group lasted up to 5 hours whereas many of the signs in the combination group (when signs were displayed) lasted only 2-3 hours. In this experiment, therefore, adding imidacloprid (even at a far higher imidacloprid:flumethrin ratio than exists in the Seresto® collar) did not increase the rate, severity, or duration of adverse effects over and against flumethrin alone in mammals. **The study is therefore evidence that the synergy seen in insects does not extend to mammals.**

- The DEFRA (2019) report on which Dr. Klement relies confirms this interpretation, noting that "[n]o additive or synergistic effects of a combination of imidacloprid and flumethrin became evident in an acute oral toxicity study in rats." Thus, Dr. Klement's claim that the DEFRA report "does not contain any report of the results of an experiment that examined the dosage of combining these substances in mice and rats" **is inaccurate**.

No studies were identified that have demonstrated additive or synergistic activity between imidacloprid and flumethrin in laboratory animals or target species *in vivo*. Thus, **there is no evidence that imidacloprid and flumethrin exert an additive or synergistic adverse effect in target animals**. However, there are multiple studies in dogs and cats that have demonstrated the safety of the combination when used as directed in the form of the Seresto® collar. In fact, as discussed in more detail below, safety studies have shown that the combination is safe even when the dosage is exaggerated through concurrent wearing of multiple collars. In addition to safety studies, there are numerous efficacy studies in both dogs and cats that, in addition to assessing the ability of the combination to effectively control fleas and ticks, also were obligated to report any significant adverse effects noted during the duration of the study. Again, these are addressed in more detail below.

To further support the safety of the combination of flumethrin and imidacloprid, there are studies which have looked at the efficacy of products containing permethrin and imidacloprid (Castilla-Castano *et al.*, 2019) in dogs. Because permethrin acts through a mechanism identical to flumethrin's, one would expect the same kind of synergy between imidacloprid and permethrin as one would expect from imidacloprid and flumethrin. The Castilla-Castano study used a spot-on product with 10% imidacloprid and 50% permethrin, which are not only higher than the percentages used in the Seresto® collar but delivered directly to the skin all at once rather than slowly released from a collar matrix as is the case for

the Seresto® collar. Permethrin and flumethrin have similar $LD_{50}$ values. These studies did not demonstrate any potential toxicity concerns for dogs.

**Safety Evaluation: Exposure Assessments**

Irrespective of the degree of exposure to a chemical, in the case of Seresto® where the active ingredients are delivered to the skin, it is the amount of chemical that reaches a target site that causes a beneficial or adverse effect. In the case of flumethrin and imidacloprid, the target sites affect nerve impulse conduction; although the doses delivered by Seresto® are not sufficient to cause harm in target animals (as I explain above); even much higher doses would not exert an effect without reaching the relevant target sites. In order to reach relevant target sites in an animal wearing a Seresto® collar, the active ingredients must be released from the collar matrix onto the skin, then be absorbed through the skin into the systemic circulation.

As mentioned previously, a relatively low dose of Seresto® is delivered from the collar to the skin surface each day. Moreover, dermal penetration of flumethrin and imidacloprid is low. Studies looking at the release of the active ingredients in Seresto® collars have been conducted so that exposures based upon skin doses can be determined. There is an initial higher release of the insecticides which declines over the life of the collar.

In cats, serum imidacloprid concentrations declined from day 7 and by 210 days no detectable imidacloprid was present (Delport, 2010a [Report ID 35642]). Similar results were noted in dogs, with initial serum imidacloprid concentrations peaking at day 7 and declining thereafter. After 3 months, average serum values fell below the detection limit (Delport, 2010b [Report ID 35643]). By 210 days, no imidacloprid was detected in any individual.

In a cat study, over the length of the 6-month study, only 4 of 16 cats had detectable flumethrin serum concentrations (one on day 14, one on day 21, and two on day 30) (Delport, 2010a [Report ID 35642]). All other serum samples tested had < 10 µg/L (analytical detection limit). In a similar 6-month long study in dogs, only two of 16 dogs had detectable serum flumethrin concentrations during the study (both at 59 days of collar wear) (Delport, 2010b [Report ID 35643]).

Additional, more sensitive testing was performed in a subsequent experiment on dogs that focused on the first seven days after collar application (Fraatz, 2017). That testing revealed that both serum flumethrin and serum imidacloprid concentrations peaked at between 120 and 144 hours (i.e., 5-6 days). Notably, although imidacloprid was detected at low concentrations in the first few hours after collar application and rose considerably over the course of the first 24 hours, flumethrin remained below the detection limit in all dogs until 24 hours and in several of the dogs was not detected until 120 hours post-application.

- Dr. Klement observes that Karen McCormack, formerly of the EPA, testified in June 2022 that there had been no studies on the rate at which the active ingredients appear in the blood of an animal wearing a Seresto® collar. To be specific, she testified that "they did not conduct a study that measures the amount of pesticide that gets in the blood of treated dogs and cats." (Appendix 15 to the Amended Motion to Certify the Filing as Class Action, p. 13). That testimony was inaccurate when made in 2022 and remains inaccurate today, as the above-described studies demonstrate.

Because any effect on the most likely target system (i.e., the nervous system) would require the active ingredients in Seresto® to enter the systemic circulation, these serum studies have two important implications. First, neither flumethrin nor imidacloprid accumulated over time despite the continued release of the active ingredients. Once the active ingredients reach a peak concentration at around 5-6 days after collar placement, they are being cleared from the system as rapidly (or more rapidly) than they are being introduced. The lack of any accumulation suggests that sequential collar use should not be problematic. Second, because serum concentrations are highest in the early weeks of collar wear and decline thereafter, one would expect any neurological or other systemic effects that are attributable to Seresto®'s chemical composition to be most frequent in the first week or two after collar placement and comparatively rare thereafter. Thus, the duration of collar wear is important to consider when evaluating causation in individual cases. Adverse events occurring more than 30 days after collar application due to its active ingredients are even more questionable than those occurring in the first two weeks. Likewise, because the active ingredients take 24 hours or more to approach their maximum concentrations (which are reached only after 5-6 days), adverse events that occur within hours of collar application are unlikely to be related to the active ingredients. Dr. Klement has speculated that other unknown collar constituents, considered to be trade secrets, could be contributing to the occurrence of adverse events either directly or in combination with the active ingredients. Suffice it to say that such comments are indeed merely speculation. Moreover, Dr. Klement cites to a 2014 Safety Data Sheet for the Seresto® collar (https://datasheets.scbt.com/sc-395480.pdf), which lists certain toxicology information for a "tradesecret" ingredient (of which the only values indicating toxicity were moderate skin irritation in rabbit testing and an acute intravenous $LD_{50}$ for mice of 23 mg/kg). He does not cite the 2020 version of the Safety Data Sheet (https://assets.elanco.com/8e0bf1c2-1ae4-001f-9257-f2be3c683fb1/ef9c3197-c508-4b6d-b750-786aae16a87a/Seresto.pdf). Comparison of the two versions shows that the "tradesecret" ingredient is stearic acid, a C18 fatty acid, which comprises between 1-5% of the collar. Stearic acid is listed among those chemicals that the U.S. Food and Drug Administration considers "generally recognized as safe" (GRAS) for use in food products. It is commonly used in detergents, soaps, and other cosmetic products and is naturally occurring in animal fats and vegetable fats (to lesser degree). Stearic acid has been shown to have low toxicity following ingestion or dermal application (Expert Panel, 1987). There is no reason to infer that stearic acid acts additively or synergistically with the active ingredients in the Seresto® collar or that its inclusion in the collar matrix would cause any adverse effects other than, perhaps, local skin irritation (assuming that a meaningful amount of the chemical is released from the collar, which to my knowledge has not been shown to be the case).

**Safety Evaluation – Clinical and Field Studies**

A number of studies have been conducted on target animals and establish a favorable safety profile. The results corroborate the toxicological analysis above. These studies have been conducted at multiple sites in the United States (e.g., the Madsen studies discussed below), South Africa (e.g., the Delport studies discussed below), Germany (e.g., the studies by Rass and Stanneck discussed below), Italy (e.g., the Brianti studies discussed below), and Ireland. Indeed, as Dr. Klement acknowledges, the DEFRA assessment (DEFRA, 2019) on which he bases his critiques of several studies concluded that **"[i]t has been shown that the product can be safely used in the target species" and that "[t]olerance of dogs and cats even to multiple collars was generally good."**

- Adult cat safety study (Madsen, 2010a [Report ID 33800]): 30 cats aged 9.5-9.7 months were randomly assigned to receive no collar (6 cats), five concurrently-worn vehicle-only collars (i.e., no-medication placebo collars; 6 cats), one Seresto® collar (6 cats), or five concurrently-worn Seresto® collars (12 cats). Notably, the cats in the 5x Seresto® collar group had their collars replaced on days 14, 28, and 42 with new Seresto® collars to maximize exposure; as discussed elsewhere in greater detail, Seresto® collars release the active ingredients at a slightly faster rate in the first month of wear. Experimental conditions were maintained for 61 days, followed by a one week "recovery period" during which the cats that had worn five collars simultaneously wore just one (whether placebo or Seresto®, corresponding to what they wore during the first 61 days). Daily clinical observations were performed, and no adverse reactions or mortality were observed. Clinical observations included mild signs of abnormal feces, emesis, and ocular discharge, but these were observed in all treatment groups without a pattern indicative of relationship to Seresto®. Physical examinations were performed by a veterinarian on days 13, 30, 47, and 61 following collar application and were normal at all times. Local skin and hair abnormalities were noted in some cats wearing five collars simultaneously and one cat in the no-collar control group, but no local abnormalities were observed in the 1x Seresto® collar group. **The author concluded, and I agree, that no adverse treatment-related findings were observed in these adult cats even when treated with an exaggerated dose (through multiple concurrent collar wear and increased frequency of collar replacement) for 61 days.**

- Kitten safety study (Madsen, 2010b [Report ID 33824]): 48 kittens aged 68-71 days (i.e., 10 weeks) and ranging from 0.774 kg to 1.466 kg were randomly assigned to receive no collar (6 kittens), five concurrently-worn placebo collars (6 kittens), one Seresto® collar (12 kittens), three concurrently-worn Seresto® collars (12 kittens), or five concurrently-worn Seresto® collars (12 kittens). Again, to maximize exposure, each kitten wearing a Seresto® collar (1x, 3x, or 5x) had the collar(s) replaced on days 29, 90, and 148. Collars were removed from all kittens at 180 days. Clinical observations were made twice daily throughout the study, and only two adverse events were noted: one cat in the 5x placebo collar group died due to what was deemed idiopathic hypertrophic cardiomyopathy (a heritable condition) based on post-mortem examination, and another cat in the 1x Seresto® collar group experienced transient acute respiratory distress. Neither was deemed treatment related, and no adverse events were noted in the 3x or 5x Seresto® collar groups. Physical examinations were performed by a veterinarian on days 15, 29, 61, 90, 120, 148, and 180 following collar application and were normal at all times. Local skin and hair abnormalities were noted in a number of cats but increased steadily with the number of collars concurrently worn, with equal rates of abnormalities for the 5x placebo group (3/6 cats) and 5x Seresto® group (6/12 cats). **The author concluded, and I agree, that no adverse treatment-related findings were observed in these kittens even when treated with an exaggerated dose (through multiple concurrent collar wear and increased frequency of collar replacement) for 180 days.**

- Target animal safety study in cats (Delport, 2010c [Report ID 33697]): 32 cats of at least 6 months in age were randomly assigned to receive no collar (8 cats), one Seresto® collar (8 cats), three concurrently-worn Seresto® collars (8 cats), or five concurrently-worn Seresto® collars (8 cats). Collars were replaced on days 59, 120, and 181, thus still further increasing the exposure.

General health observations were made daily, with clinical examinations made on study days 8, 14, 31, 59, 118, 178, and 240. Adverse events were noted in about half of the cats in each group, with no obvious pattern indicative of relationship to Seresto® for any adverse event (upper respiratory disease was observed only in cats wearing 3x or 5x Seresto® collars, but there was no clear dose-response and no plausible mechanism by which Seresto® collars would cause this outcome). Clinical signs included vomiting, salivation, and eye discharge (among others that would not plausibly have been related to the active ingredients in Seresto® collars). However, vomiting was observed as frequently in the no-collar control group as in any other group. Salivation was observed in all groups but was as frequent in the 1x Seresto® group as in the 5x Seresto® group, suggesting a lack of dose-response that would mean the active ingredients were not causing the salivation. Eye discharge was observed during clinical examinations only in the 3x Seresto® group, again suggesting a lack of dose-response and no relation to the active ingredients; moreover, eye discharge was observed during general health observations for all groups without obvious dose-response. General health observations also included two cats displaying depression, one in the 1x Seresto® group and one in the 5x Seresto® group; due to the low rate and lack of a dose-response, I do not believe this observation was related to the active ingredients in Seresto®. **The author concluded, and I agree, that there were no clinically significant treatment-related changes observed in these adult cats even when treated with an exaggerated dose (through multiple concurrent collar wear and increased frequency of collar replacement) for 240 days.**

- Adult dog safety study (Madsen, 2010c [Report ID 33805]): 30 beagle dogs aged 10.3-11.2 months were randomly assigned to receive no collar (6 dogs), five concurrently-worn placebo collars (6 dogs), one Seresto® collar (6 dogs), or five concurrently-worn Seresto® collars (12 dogs). The dogs in the 5x Seresto® collar group had their collars replaced on days 14, 28, and 42 with new Seresto® collars to maximize exposure. Experimental conditions were maintained for 61 days, followed by a one week "recovery period" during which the dogs that had worn five collars simultaneously wore just one (whether placebo or Seresto®, corresponding to what they wore during the first 61 days). Daily clinical observations were performed, and no adverse reactions or mortality were observed. Clinical observations included mild signs of ocular discharge, emesis, abnormal feces, and inter-digital cysts but were observed in all treatment groups without a pattern indicative of relationship to Seresto®. Physical examinations were performed by a veterinarian on days 13, 30, 47, and 61 following collar application and were normal at all times. Local skin and hair abnormalities were noted in some dogs wearing five collars simultaneously, with similar rates in the 5x placebo group (2/6 dogs) and 5x Seresto® group (5/12 dogs). **The author concluded, and I agree, that no adverse treatment-related findings were observed in these adult dogs even when treated with an exaggerated dose (through multiple concurrent collar wear and increased frequency of collar replacement) for 61 days.**

- Puppy safety study (Madsen, 2010d [Report ID 33806]): 48 beagle puppies aged 48-50 days (i.e., 7 weeks) and ranging from 1.529 kg to 2.963 kg were randomly assigned to receive no collar (6 puppies), five concurrently-worn placebo collars (6 puppies), one Seresto® collar (12 puppies), three concurrently-worn Seresto® collars (12 puppies), or five concurrently-worn Seresto®

collars (12 puppies). Again, to maximize exposure, each puppy wearing a Seresto® collar (1x, 3x, or 5x) had the collar(s) replaced on days 29, 90, 125, and 148. Collars were removed from all puppies at 180 days. Clinical observations were made twice daily throughout the study, and only one adverse event was noted: one puppy in the no-collar control group suffered a mild seizure. No adverse events were noted in the 1x, 3x, or 5x Seresto® collar groups. Clinical observations included mild signs of ocular discharge, emesis, and abnormal feces but were observed in all treatment groups without a pattern indicative of relationship to Seresto®. Physical examinations were performed by a veterinarian on days 15, 29, 61, 90, 120, 148, and 180 following collar application and were normal at all times. Local skin and hair abnormalities were noted at roughly equal frequency in all puppies that wore at least one collar, with equal rates of abnormalities for the 5x placebo group (5/6 puppies) and 5x Seresto® group (10/12 puppies). **The author concluded, and I agree, that no adverse treatment-related findings were observed in these puppies even when treated with an exaggerated dose (through multiple concurrent collar wear and increased frequency of collar replacement) for 180 days.**

- Target animal safety study in dogs (Delport, 2010d [Report ID 33692]): 32 mixed breed dogs of at least 6 months in age were randomly assigned to receive no collar (8 dogs), one Seresto® collar (8 dogs), three concurrently-worn Seresto® collars (8 dogs), or five concurrently-worn Seresto® collars (8 dogs). Collars were replaced on days 62, 119, and 181, thus still further increasing the exposure. General health observations were made daily, with clinical examinations made on study days 1, 8, 14, 30, 59, 118, 182, and 240. Adverse events were noted in only two dogs, one of which developed wet eczema in its left front foot (1x Seresto® group) and one which developed chronic kidney disease (3x Seresto® group). Neither was deemed treatment-related. I agree that neither has an obvious relation to Seresto®, particularly given the lack of any dose-response, the lack of a plausible model of causation, and the lack of similar findings in other studies. Clinical signs included lacrimation and dry feces (among others that would not plausibly have been related to the active ingredients in Seresto® collars). Dry feces was observed in only one dog in the study (3x Seresto® group), suggesting no dose response and no relation to Seresto®. I address lacrimation below. Additional general health observations included nonspecific digestive issues such as vomiting and fecal changes, but there was no dose response observed (indeed, no such signs were observed at all in the 5x Seresto® group). **The author concluded, and I agree, that there were no clinically significant treatment-related changes observed in these adult dogs even when treated with an exaggerated dose (through multiple concurrent collar wear and increased frequency of collar replacement) for 240 days.**

    - Lacrimation (epiphora) was observed only in the Seresto® groups but did not correlate well with dose; two dogs in the 1x group showed lacrimation, but one had lacrimation solely on the day before the Seresto® collar was placed (i.e., while the dog was not being exposed to Seresto® and was effectively a control). One dog in the 3x group and 3 dogs in the 5x group displayed lacrimation as well. Moreover, all instances of lacrimation occurred in either beagles or a border collie cross and were deemed breed-appropriate. The study inclusion criteria were indifferent to breed, so it would not be surprising to see increasing lacrimation with increasing Seresto® dosage if breeds with a

greater propensity for lacrimation happened to be increasingly prevalent in the groups randomly assigned to receive progressively greater doses of Seresto®. It is therefore worth comparing these results to other studies in which breed was uniform throughout the study population. In all but one of the dogs that displayed lacrimation while wearing at least one Seresto® collar in this study, lacrimation was seen during at least three clinical examinations within the first 60 days of the study; by comparison, the studies described above (Report ID 33805 and 33806) likewise tracked lacrimation (there denoted as "ocular discharge") over this same time period but used exclusively beagle dogs and showed no dose response. Thus, it seems likely that the group-to-group variation in lacrimation seen in this study can be explained by differences in breed. The author agreed.

I note that Dr. Klement, apparently importing the DEFRA (2019) analysis directly into his report, voiced concern over the existence of depression, vomiting, changes in food consumption, eye secretions, change in food intake, and diarrhea in these studies. As I discuss above, though, **there is not even a strong association between the rate of those observations and degree of Seresto® exposure**. Some of those signs occurred with similar frequency in the control group. Others occurred only in Seresto®-treated animals, but occurred with such low frequency that one cannot rule out that their appearance in the Seresto®-treated group rather than the control group was mere chance (which is further supported by the lack of increasing frequency with higher doses of Seresto®). I explain above that even when one has demonstrated an association between treatment and effect, one must then investigate further to establish causation. **Here, though, the studies do not even show a clear association worthy of further investigation.**

Additional evidence of safety comes from efficacy studies, in which safety was a secondary endpoint. Animals enrolled in the studies were routinely evaluated by trained veterinarians who reported adverse effects. For example:

- Rass & Stanneck (2010a) (Report ID 35644): 346 privately-owned cats that were either naturally infested with at least three ticks or five fleas or were living with an infested cat were enrolled in a field study and randomly assigned to receive either a Seresto® collar (256 cats) or a control collar (90 cats). All cats were monitored by their owners, and the infested cats were additionally examined in the clinic on days 2, 28, 56, 84, 112, 140, 168, 196, 224, and 238 after collar placement. The Seresto® collar was shown to have superior efficacy compared to the control collar containing diazinon (also known as dimpylat), an organophosphorous insecticide with insecticidal activity unrelated to the active ingredients in Seresto®. The rates of both total adverse events and potentially treatment-related adverse events (including events of "likely, possibly, or unclassified" relation to the collar at issue) were similar for Seresto® and the control collar, with no statistically significant difference in the groups. Nearly all of the adverse events considered potentially treatment-related were local skin effects, and others were of questionable relation (e.g., vomiting blood and diarrhea). Only one serious adverse event was reported as related to treatment, an incidence of moderate contact dermatitis with alopecia and pruritis (i.e., a local skin effect that was likely mechanical in nature). **There is no evidence from the study that the active ingredients of Seresto® caused any adverse events.**

- Rass & Stanneck (2010b) (Report ID 35645): 422 privately-owned dogs meeting the same criteria as the above-described cat study were randomly assigned to receive a Seresto® collar (286 dogs) or a control collar (Dimpylat/diazinon; 136 dogs). The monitoring protocol for the dog study was the same as the cat study described above. Again, the Seresto® collar was shown to be superior to the control with regard to efficacy. There were numerically fewer total and treatment-related adverse events in the Seresto® group than in the control group, though the difference was not statistically significant. Only three adverse events were deemed treatment-related in the Seresto® group, and all three were local skin/hair effects at the collar application site. **There is no evidence from the study that the active ingredients of Seresto® caused any adverse events.**

The results of many of these studies were subsequently published in the peer-reviewed scientific literature. For example, the efficacy studies discussed above were later published as Stanneck *et al.* (2012a), which showed no statistically significant difference between the Seresto® and control group with regard to adverse events (as Dr. Klement acknowledges). All studies were conducted to meet regulatory requirements such as following Good Clinical Practices, Good Laboratory Practice for Nonclinical Laboratory Studies, EPA Companion Animal Safety Guidelines, and VICH GL 43 (Target Animal Safety).

Still further evidence of safety comes from additional large field studies conducted on animals wearing Seresto® collars. **Each of these studies confirmed that Seresto® is highly effective against fleas and ticks as well as safe; my focus here is directed to the safety findings:**

- Brianti *et al.* (2013): 82 shelter dogs of mixed breeds in Italy (Lentini) wore a Seresto® collar and were followed for 250 days. One dog was noted to have local dermatitis at the collar site (likely a mechanical, not chemical, effect) that reversed within two weeks after the collar was removed. No other adverse events were noted; although the methods section does not describe the monitoring protocol, the dogs were examined by trained personnel closely enough at least to investigate for fleas and ticks on days 0, 2, 7, 14, 30, 45, 60, 75, 90, and 250 of the study.

    - Of further note, the collars were highly effective against fleas and ticks in this study. The tick and flea burden on the dogs at the beginning of the study was described as so severe that volunteers "were scared to go through infested pens." From day 14 of the study onward, however, ticks were completely absent for five of the seven examination dates (one dog was tick-positive on one examination date, and two were tick-positive on another) and fleas were absent for six of the seven dates (two dogs were flea-positive on one examination date).

- Brianti *et al.* (2014): 219 dogs of various breeds at two different shelters in Italy (Messina and Augusta) were randomly assigned to either an untreated control group (117 dogs) or a group that received Seresto® collars (102 dogs). Although some of the dogs in the Seresto® group were adopted, excluded due to loss of the collar, or died during the study period due to unrelated causes (e.g., fatal injuries while fighting with other dogs), all 102 dogs remained in the study at the 90-day follow-up and 84 dogs remained in the study at the 300-day follow-up. Attrition was more severe in the control group, with all 117 dogs available at 90-day follow-up

but only 67 available at 300-day follow-up. All dogs in the study were subject to a physical examination and blood testing at study days 0, 90, 180, 210, and 300, with additional skin tissue sampling at days 0, 210, and 300 and bone marrow sampling at days 0 and 300. **Additionally, "[a]ll dogs included in the study were observed daily for any changes in their health." No adverse effects related to the collar were observed.**

- I note that Dr. Klement discusses this paper in his report and argues that the shelter animals were not observed as closely as they would have been if they were privately owned. I disagree with his implication. Although shelter dogs might be given less individual attention than privately owned dogs in general, the dogs in this study were assessed by trained veterinary personnel on a daily basis specifically to evaluate changes in their health.

- Dr. Klement also argues that the lack of minor skin effects noted in the study suggests a lack of rigor in the reporting and/or observations. I disagree. This same group reported a local adverse effect in Brianti *et al.* (2013). Another study by this same group (Brianti *et al.* (2016), which Dr. Klement does not discuss but which I discuss below) followed 55 Seresto®-treated dogs as well as 60 dogs bearing Scalibor® collars (deltamethrin active ingredient) for 310 days using a similar daily observation protocol. Although they observed local skin effects in three dogs assigned to the Scalibor® group, they did not observe any abnormalities in the 55 Seresto®-treated dogs. These studies collectively demonstrate that the authors were observing the dogs closely enough to observe and report local skin effects had they occurred. Dr. Klement's citation to higher rates of skin effects and cutaneous injuries reported in studies on cats does not suggest otherwise, as cats groom themselves more meticulously than dogs (including collar-licking, as Dr. Klement discusses). This could explain why this same group observed local skin reactions in 3.8% of Seresto®-treated cats in Brianti *et al.* (2017) but only 0.4% (1/239) of the Seresto®-treated dogs in Brianti *et al.* (2013), Brianti *et al.* (2014), and Brianti *et al.* (2016).

- Brianti *et al.* (2016): 224 dogs of mixed breeds at four different shelters in Italy (all in Sicily) were randomly assigned to receive Seresto® collars (55 dogs), Scalibor® collars (60 dogs), CaniLeash® vaccination (54 dogs), or no treatment (control group, 55 dogs). All 55 dogs in the Seresto® group completed the seven-month study, during which they were clinically evaluated and checked for fleas and ticks at 120, 210, and 360 days; skin and blood samples were taken at these visits, and bone marrow was sampled on days 210 and 360. Moreover, "[a]ll dogs included in the study were observed daily for any changes in their health and abnormal health conditions were recorded." Although three of the dogs wearing Scalibor® collars developed local skin lesions at the collar site, **no abnormalities were noted in the 55 Seresto®-treated dogs.**

- Brianti *et al.* (2017)/Greco *et al.* (2019): These two publications both report on a study of 204 privately owned cats on the Italian islands of Lipari and Vulcano. Cats were randomly assigned to receive Seresto® (104 cats) or left untreated (100 cats). The study lasted 360 days, with

collars being replaced at day 210 of the study such that cats wore two collars consecutively. Seventy-nine Seresto®-treated cats completed the study; of those that did not complete the study, only one was excluded due to a suspected adverse effect of Seresto® (an ulcerative cutaneous inflammation at the collar application site, discussed further below). The owners of the study cats were Instructed to observe the cats daily and report any abnormalities in the general health of the cats. Additionally, all cats were clinically examined on study days 210, 270, and 360. Local skin reactions were observed in 3.8% of Seresto®-treated cats, with all reactions being noticed in the first four weeks of the study and all but one reaction resolving spontaneously after merely loosening the collar. **No other adverse events were evaluated as being related to Seresto®. At the study closure, all cats were in good general health.**

- As Dr. Klement notes, **one** Seresto®-treated cat experienced ulcerative cutaneous inflammation and was removed from the study. However, there is no reason to ascribe this local skin reaction to the active ingredients in Seresto® rather than the mere application of a collar. It is well known that wearing a collar, regardless of the collar's composition, can cause irritation and even ulcers on occasion.

- Dr. Klement also notes that there were more deaths in the Seresto®-treated group than in the control group. **This is only half true, and it is misleading**. First, Dr. Klement apparently did not review Greco *et al.* (2019), which was a follow-up study conducted by the same research group on the same study population of cats. Although Brianti *et al.* (2017) reported six deaths in the Seresto®-treated group versus three in the control group, Greco *et al.* (2019) reported six and *nine* deaths, respectively (i.e., all-cause deaths were more frequent in the control group than in the Seresto®-treated group). Second, as Dr. Klement notes, some deaths were due to trauma; specifically, almost half of the deaths reported in the initial paper (four of nine) were due to "car trauma." Others were likewise due to causes with no logical connection to Seresto® (three deaths due to suspected infectious disease, one due to respiratory failure, and one due to aortic thromboembolism). While it is not clear which group experienced which deaths, I note that the Seresto®-treated cats in the study were on average nine months older than the control cats; if there was a modestly higher rate of non-trauma deaths in that population, it would not necessarily be surprising. **There is no basis on which to conclude that Seresto® played any role in any of the deaths or to question the authors' conclusion that "no adverse effects [other than the local skin reactions] were evaluated as being product related."**

In 2018, Cyton Biosciences analyzed the then-available studies on the Seresto® collar (Cyton Biosciences, 2018). By Cyton's account, 530 cats and 527 dogs had been treated with Seresto® in studies conducted prior to marketing of the collar in the United States. Another 476 cats and 840 dogs had been treated with Seresto® in studies conducted thereafter. Not a single treatment-related adverse drug reaction (i.e., related to the active ingredients) was observed. **This summary of the clinical studies is consistent with my evaluation of the studies described above and confirms the safety of the Seresto® collar.**

The suggestion has been made that AE would not have been predicted based upon pre-market target animal safety studies. While individual laboratory studies generally used small groups of dogs or cats, it

is important to point out that field efficacy studies enrolled many more animals. Thus, looking at small numbers of animals in a single study and suggesting that the study was too small to identify a potential adverse event is misleading.

**Summary of Studies**

**As described above, over 2,300 Seresto®-treated animals have been evaluated in studies. No adverse effects related to the active ingredients of Seresto® were reported in these animals. Even if this alone does not exclude the possibility that Seresto®'s active ingredients cause rare side effects (that simply did not occur in any of the studies), it combines with the toxicological assessment I provide above to suggest that Seresto® is indeed safe.**

**Safety Evaluation – Veterinary Literature Reports**

It is interesting that there are almost no case reports in the peer-reviewed veterinary literature associating the use of a Seresto® collar with AEs. Only one case report was found that described a significant dermatitis (superficial suppurative necrolytic dermatitis) in a miniature schnauzer associated with the use of a Seresto® collar (Loewinger *et al.* 2022). The reaction occurred in a breed known to rarely show similar reactions to shampoo. There are no known case reports in the veterinary literature suggesting the collar as contributing to the death of a pet. It seems unlikely that individual cases or case series would not have been published if AEs were being encountered by veterinary professionals as frequently as would be suggested by claims being advanced in litigation.

Anecdotally, veterinarians have reported safe and effective use of the Seresto® collar and have been surprised about AE reports. In addition, one of the two national pet poison helplines (Pet Poison Helpline) assessed the risk of AEs based upon calls received and came to the conclusion that there was no excessive risk of an AE.

**Adverse Event Reports**

Significant attention has been given to the fact that the Seresto® collar was not approved for use in Canada based upon an evaluation of significant AEs by the Pest Management Regulatory Agency (PMRA) of Health Canada. The PMRA is responsible for pesticide regulation in Canada. Unfortunately, in the case of the Seresto® collar, the methodology used to evaluate the AEs is not publicly available to determine whether it was a stringent and science-based evaluation. To my knowledge no final report is available for examination. Although PMRA reportedly concluded that use of the Seresto® collar is associated with a number of pet deaths and other AEs, that conclusion remains unexplained, isolated, and inconsistent with the results of toxicology studies, safety studies, veterinarians' experience, and regulatory evaluations by numerous other agencies around the world. But, as I discuss above, USEPA has reviewed the same set of death reports as PMRA and concluded that none were attributable to the active ingredients in Seresto®. In fact, in July 2023 USEPA carefully evaluated all of the evidence (including PMRA's analysis, about which USEPA had more details than have been publicly disclosed) and rejected a call for the Seresto® collar to be removed from the market. I am not aware of any other regulatory agencies around the world crediting PMRA's analysis and choosing not to approve Seresto® collars.

There are a number of peer-reviewed publications discussing the approaches to and the strengths and weaknesses of incident reporting systems (Naranjo *et al.*, 1981; Edwards *et al.*, 2000; Maddison and

Page, 2008; Macrae, 2016; Coleman and Pontefract, 2016; Mascolo *et al.*, 2017; Pacurariu *et al.*, 2017; Shakib *et al.*, 2019; Monnot *et al.*, 2021). Suffice it to say that there is no standardized ideal incident reporting (pharmacovigilance) scheme. As Maddison and Page (2000) point out, one of the great challenges in determining the incidence of adverse drug reactions ("ADR") is the difficulty in accurate identification of an ADR. Experienced clinicians and experts have been shown to agree less than 50% of the time when assigning causality to an ADR (Maddison and Page, 2000). Reported clinical signs are often non-specific (e.g., vomiting, diarrhea, anorexia) and rarely pathognomonic for an ADR. In many well controlled studies, the frequency and nature of ADRs are similar in drug-treated and placebo-treated groups. In addition, for veterinary related reports baseline breed, age, or sex information regarding the occurrence of specific clinical signs (e.g., seizures) or specific disease conditions (e.g., cancer) is not considered.

Many factors can be associated with increased rates of reporting including: the novelty of the reaction, severity of the reaction, a limited time that the drug/chemical has been on the market, media coverage, and litigiousness of the complainant (Maddison and Page, 2008). When an association is observed between drug/chemical exposure and an ADR, a number of considerations help to categorize an ADR into probably, possible, unclassified, and unlikely categories. These considerations should include 1) the strength of the association, 2) the consistency of the association, 3) the specificity of the association, 4) the temporality of the association, 5) the biological gradient or dose-response, 6) the plausibility of the association, 7) the coherence of the association, 8) experimental evidence, 9) analogy, 10) possible alternative hypotheses and lastly 11) quality (how complete, reliable, and rigorous is the evidence of the suspected AE).

*Pet Owner vs. Veterinary Reports*

Data was not available to know how many AEs were reported by veterinarians or pet owners. This is a critical piece of information to be able to judge whether an AE was more likely due to product exposure or not. A report directly from a pet owner would not carry the same weight as a report that has been evaluated and communicated by a veterinarian, particularly in those situations where the veterinarian conducted a thorough clinical evaluation. Irrespective of whether an AE came from a veterinarian or a pet owner, the etiology for a death in the absence of a thorough post-mortem examination is often difficult to determine with certainty.

*Assessing Causation in Adverse Event Reports*

Assessment of causation as to adverse events is a very individualized pursuit that depends on detailed knowledge of an animal's history and treatment course. As noted above, characteristics of individual animals such as breed, sex, and weight can play a profound role on the individual's baseline risk of experiencing an adverse event (see, e.g., Erlen *et al.*, 2018). Moreover, a thorough history needs to be available for assessment including the environment of the pet, dietary history, vaccination status, etc. as these characteristics can suggest alternate causes of an adverse event. Onset of clinical signs vs. initial exposure is another critical piece of information to help assess causality. Significant adverse effects would be expected when exposure was the greatest. As noted above, release of the AI from the Seresto® collar declines over time; the highest exposure begins about a week after the application. Note that serum concentrations of the AI were generally low and they could not be detected within a short period of time in relation to the duration of collar effectiveness. Thus, AE reports weeks to months after

collar application would not be expected and a thorough consideration of alternative explanations would be warranted.

It is important to point out that the AE reporting scheme for Seresto® collars was more thorough and conservative than that typically required for pesticides. The scheme used by Bayer was one used in the EU (ABON system) to assess AE reports for veterinary drugs. The scheme requires a causality measure to be applied to an AE. Woodward (2005) suggests that deciding on what might constitute an expected or unexpected adverse reaction is not always straightforward, although the ABON scheme does require a more in-depth assessment than one which does not require a causality application. The Seresto – Review of PMRA Assessment (Cyton, 2017) discusses the use of the ABON scheme in relationship to the PMRA scheme, which is not available for scrutiny.

*Product Identification Bias*

One important fact that complicates AE reporting is the evidence for counterfeit Seresto® collars on the market. The Veterinary Information Network (VIN) is a widely accessed on-line resource of information for the veterinary profession. The issue of AE associated with the use of Seresto® collars has been highlighted several times on the VIN website. One VIN article dated March 8th, 2021 ("Seresto flea collars in complaints could be counterfeits", available at https://news.vin.com/default.aspx?pid=210&Id=10129480), states that:

> Federal regulators are unable to say whether Seresto pet flea collars cited in tens of thousands of adverse incident reports are authentic product or knockoffs, according to information provided today by the U.S. Environmental Protection Agency.

The article goes on to state that:

> Last year, U.S. Customs and Border Protection seized multiple shipments of counterfeit collars from mainland China and Hong Kong. CPB warned the public that fake collars "may consist of harmful ingredients that may sicken your pet, or they may cause chemical burns or hair loss."

Absent verification that an authentic Seresto® collar was used on a pet for which an AE was reported, any causal inference must be viewed with additional skepticism.

*General Discussion of Seresto® by the Veterinary Profession*

Of note, VIN has independent veterinary toxicology consultants who provide their opinions on toxicology-related issues. In one on-line article from March 5, 2021 ("Veterinarians temper flea-collar fears raised by news report", available at https://news.vin.com/default.aspx?pid=210&Id=10124607&f5=1), two experts familiar with the concerns spurred by the adverse event reports that have led to litigation provided the following comments:

> "Looking at these reports, these are very random things, ranging from ruptured eardrums — which I can't make fit really at all — to liver failure, to heart problems, to kidney failure," said Dr. Tina Wismer, medical director at the ASPCA Animal Poison Control Center and a toxicology consultant for the Veterinary Information Network, an online community for the profession and parent of VIN News. "The fact that the signs are very random makes me think that probably [the collar] is not involved," she said.

> Dr. Sharon Gwaltney-Brant, another VIN toxicology consultant, noted that consumer reports to the EPA are unverified and often anecdotal. “Anyone can report anything to regulatory agencies — that doesn’t mean it’s true or accurate,” she said. “This is why looking at the raw data from these agencies is so dangerous — they reflect only the reports, not any ancillary information required to determine if there’s actually any merit to the report.”

In addition to the evaluation performed by veterinary toxicologists at the Pet Poison Helpline, the ASPCA Animal Poison Control Center has also received calls related to the collar. The ASPCA experience mirrors that of the Pet Poison Helpline. As the VIN article noted:

> Wismer said the ASPCA Animal Poison Control Center has fielded calls about Seresto collars since the collars first came on the market, mostly from people whose pets ate them. Her records of these reports show vomiting in 26% of cases; ataxia, or wobbliness, in 2.7%; and tremors in 1.3%.
>
> Nothing in these proportions suggests a cause for alarm, she said. Wismer added that she expects to see vomiting and neurologic signs from some animals that ingest Seresto’s active ingredients, flumethrin and imidacloprid. But the wide variety of signs attributed to the collar in the consumer reports leads Wismer to doubt that the collars are to blame.

A Journal of the American Veterinary Medical Association news article dated May 1, 2021 (Cima, 2021, available at https://avmajournals.avma.org/view/journals/javma/258/9/javma.258.9.915.xml) has the following statement from the USEPA:

> “Some incidents are well-investigated and reported in such a way as to establish a strong link between the adverse effect and the exposure,” the EPA statement says. “On the other hand, many other reports do not include enough facts to clearly demonstrate causation.
>
> “Many of the reports are anecdotal, with no indication of whether the user followed label use instructions or used a product appropriate for the pet type and size. Generally, however, there is no process for verifying the information in reports.”

An online VIN article dated July 7, 2022 (“Veterinarians puzzled by flea collar angst – News – VIN”, available at https://news.vin.com/default.aspx?pid=210&catId=-1&id=11021199) has the following statement:

> “If you poll toxicologists and the veterinarians who recommend millions of these collars … it’s a nonissue," Dr. Sharon Gwaltney-Brant, a board-certified veterinary toxicologist, told VIN News. "But in today's world, any jury or congressional committee can decree to 'know' things that science cannot support."
>
> Directors of two national animal poison centers — Pet Poison Helpline and the ASPCA Animal Poison Control Center — have reported no deaths associated with the collars.

**Evidence-Based Decision Making**

Ultimately, decisions about safety depend on the quality of evidence available. In the case of Seresto® there is only questionable adverse event reporting and interpretation to guide regulatory decision-

making, which stands alone and in contradiction to substantial evidence and other approvals from regulatory authorities regarding the safety of Seresto®. Veterinarians with specialized toxicology training have not identified a particular concern regarding Seresto® collars when used according to label directions. As mentioned earlier, AE reporting is designed to detect "signals" of possible adverse and unexpected events associated with a given exposure; AE schemes are not designed to determine their ultimate etiologies. While well designed epidemiologic studies can help strengthen an association between a chemical exposure and a given adverse outcome, they fundamentally depend on the availability of a robust dataset. Thus, any assertion that there is epidemiologic evidence to support a safety issue with the Seresto® collar can't be supported. **In fact, there is no evidence that any epidemiologic methodology was used by PMRA to reach their conclusions**.

**Inferring Causation from Association**

As I discuss above, one cannot merely assume that an adverse event has been caused by a particular treatment. That remains true even if there is a demonstrated association between the two. Yet, Dr. Klement appears to discard this basic premise when opining that Seresto® must be causing side effects because reports of side effects with Seresto® exceed the number of reports for other products. At most, that is an association. When faced with an association, one must then take the next step of evaluating causation. Instead of doing so (for example, by reviewing the toxicology data that is summarized in the DEFRA report on which he relies), Dr. Klement blindly relies on the PMRA assessments. As noted above, though, PMRA's assessment has not been released to allow scrutiny and appears to align closely with USEPA's assessment, **which now establishes that deaths that can be attributed to the Seresto® collar are quite rare, are mechanical rather than chemical in nature, and form only a very small fraction of all adverse events reported**.

Dr. Klement then concludes that, because in his view the studies he reviewed do not adequately rebut PMRA's still-unexplained findings, the manufacturer of Seresto® should have informed consumers of the side effects he believes Seresto® is causing. In so doing, he is merely **assuming** that PMRA's conclusions are accurate despite having absolutely no visibility into PMRA's methodology (and despite contrary evidence from the toxicological studies, the clinical studies, and USEPA's assessment). Moreover, as described above, USEPA's own conclusions and its disclosures regarding PMRA's conclusions seriously call into question Dr. Klement's interpretation of PMRA's conclusions. Given that neither Dr. Klement nor PMRA has explained why any of the adverse events in question should be attributed to Seresto®, and in light of my own opinions expressed above, I disagree with Dr. Klement's opinion that Bayer/Elanco should have warned consumers that Seresto® causes such adverse events.

I also disagree with Dr. Klement's overarching approach of blindly accepting PMRA's still-unsupported conclusions (which support the case of those who retained him) when the data for those conclusions have not been published and failing to carefully critique the methodology and outcomes of the multiple studies and expert opinions that support Seresto®'s safety. If PMRA had disclosed a carefully performed analysis with persuasive results suggesting causation, perhaps it would have suggested the need for further investigation. However, a still-undisclosed analysis by PMRA, based on adverse event reports that have not been identified and are not available to evaluate, should not require Bayer/Elanco to warn of adverse events when higher-quality evidence unanimously supports the safety of Seresto®.

**Bayer proved Seresto®'s safety through the toxicological and clinical studies I discuss above. Seresto®'s safety is also supported by experts at the Pet Poison Help Line and the American Veterinary**

**Medical Association, as Dr. Klement admits, as well as the DEFRA analysis Dr. Klement cites. USEPA likewise favorably evaluated the product's safety when Seresto® was first registered, and USEPA continues to support the product's safety even after carefully reviewing adverse event reports.**

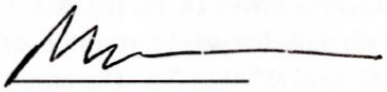
**Conclusions**

1. Each AI in the Seresto® collar, the pyrethroid flumethrin and the neonicotinoid imidacloprid, have good mammalian safety profiles when products containing them are used according to label directions. Safety has been shown in dogs and cats through numerous laboratory safety and field use studies.
2. The combination of flumethrin and imidacloprid is more effective at controlling fleas and ticks on dogs and cats than either AI used alone. Synergy between the two appears to be modest and specific to the insect nervous system. Administering the AIs in combination does not pose an increased risk to other systems (e.g., the cardiovascular or gastrointestinal system), nor does it appear to pose an increased risk to the mammalian nervous system.
3. **Numerous safety and efficacy studies, collectively involving hundreds of dogs and cats, have shown the combination to be safe when used according to label directions and even in exaggerated doses (involving the concurrent use of 5x collars and frequent substitution of fresh collars)**. Safety and efficacy studies have been conducted on puppies and kittens as well as adult dogs and cats. Many safety and efficacy studies have been published in the peer-reviewed scientific literature.
4. Seresto® collars have been approved for use in multiple countries with multiple regulatory agencies reviewing safety and efficacy studies and concluding that the product is safe and effective when used as directed.
5. Studies evaluating the release of the AIs from the collar show that the greatest release occurs within the first weeks after the collar is applied with release rates decreasing over the course of an 8-month efficacy period. Release rates result in dermal exposure to amounts of the AIs well below NOEL or NOAELs. In addition, systemically absorbed concentrations of the AIs, as measured by serum concentrations, are low or not detected; this indicates that AI concentrations at sites in the nervous system of dogs and cats would be low or not detected as well.
6. Adverse event reporting systems vary; no one system is perfect and there is the potential for multiple biases to confound interpretation of collected data. The AE system used for the Seresto® collar by Bayer/Elanco is more rigorous than that likely used by other companies; as a result, comparing data collected by one company to data collected by another company can be misleading.
7. AE reporting systems are designed to provide "signals" of potential AEs; a whole range of studies and information is generally needed to help confirm or refute a cause – effect relationship. In many (most) AE where death has occurred, extensive clinical or postmortem data is unavailable to help determine the cause. A recent assessment by USEPA of all AEs involving death in relation to the Seresto® collar concluded that none of the > 1000 reported deaths assessed was even "probably" related to the AIs in Seresto®.
8. Multiple veterinary toxicology specialists have concluded that use of the Seresto® collar is safe and effective when used according to label directions. Anecdotally, practicing veterinarians have not noted an alarming degree of AE associated with the use of the collar. There is only one

case report of a serious reaction in a dog following application of the collar. The breed of the dog is known to rarely have significant skin reactions to dog shampoos.

9. While much attention has been given to the conclusions reached by the PMRA of Health Canada which led to a decision to deny approval of the collar to be used in Canada, serious questions regarding the methodology used for the assessment have been raised. The lack of transparency regarding the methodology used make independent evaluation of their conclusions difficult.
10. It is not possible to make any conclusions regarding causation of alleged symptoms experienced by any pet exposed to a Seresto collar® without an individual assessment of the pet's veterinary history and individual circumstances. This includes the need to evaluate each adverse event individually against the background risk the animal faced had the collar not been used. There are individual risk factors that significantly impact the background risk an animal faces. Those individual risks must be accounted for when assessing the cause of an adverse event in a particular animal. It is scientifically unsound to assume causation in any individual animal without evaluating that animal's individual characteristics and veterinary course.
11. **Multiple lines of evidence support the conclusion that the Seresto® collar is safe to use on dogs and cats when used according to label directions**.
12. Per my review of the evidence described in this report, I do not believe that even a single animal's death can be attributed to exposure to Seresto's active ingredients when using the collar as directed.

Respectfully submitted:



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