Message

From: Kibilov, Nicholas [Kibilov.Nicholas@epa.gov]
Sent: 3/2/2021 9:52:04 PM
To: AO OPA OMR CLIPS [AO_OPA_OMR_CLIPS@epa.gov]
Subject: Daily News Clips: Afternoon Edition, 3/2/21

Daily Media Clips: March 2, 2021 (afternoon edition)

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News-PressNow: $48 million Blacksnake Creek project nearing completion
NYT: Did Trump Really Make Dishwashers Great Again?
Daily Inter Lake: EPA approves new selenium standards for Lake Koocanusa
Storm Water Solutions: EPA FINALIZES ALLOCATION FORMULA FOR SEWER OVERFLOW AND STORMWATER REUSE GRANTS PROGRAM
Water Technology: EPA settles case with Washington seafood processor over discharge violations

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Steel Dynamics agrees to upgrade emissions equipment, pay EPA settlement fee
https://wpta21.com/2021/03/02/steel-dynamics-agrees-to-upgrade-emissions-equipment-pay-epa-settlement-fee/
March 2, 2021

CHICAGO (WPTA21) – A northeast Indiana steel producer agreed to upgrade their air pollution control equipment and pay a settlement fee to the state and federal governments.

The EPA announced a settlement with Steel Dynamics, Inc. (SDI) Tuesday morning.
Federal regulators accused SDI of violating the Clean Air Act by not properly capturing emissions from two facilities in Butler, Indiana.

Inspectors said they found multiple violations at the Iron Dynamics Division and Flat Roll Division.

The emissions contain microscopic particles that can cause serious health problems if inhaled.

As part of the settlement, SDI agreed to upgrade equipment that would reduce air emissions. The upgrade is expected to cost $3 million, according to the EPA.

The company also agreed to pay a $475,000 civil penalty that will be split evenly by the Indiana and federal governments.

Learn more about the Clean Air Act here.

Steel Dynamics to pay $475,000 penalty, reduce air pollution as part of EPA settlement
https://www.wane.com/news/local-news/steel-dynamics-to-pay-475000-penalty-reduce-air-pollution-as-part-of-epa-settlement/
Posted: Mar 2, 2021 / 11:53 AM EST / Updated: Mar 2, 2021 / 11:53 AM EST

CHICAGO (WANE) Steel Dynamics, Inc. will spend $3 million to upgrade air pollution control equipment at its facilities in Butler, Indiana as part of a settlement announced by the EPA involving alleged violations of the Clean Air Act.

According to a news release issued by the EPA Tuesday morning, it's alleged that multiple violations were found by the EPA during an inspection and record review of Steel Dynamics' Iron Dynamics Division and Flat Roll Division plants in Butler.

The violations included a failure to capture all emissions from three ladle metallurgical stations and route them to a baghouse, as required by the company's Title V operating permit. The failure to control those emissions resulted in excess emissions of particulate matter which contains microscopic solids that are so small that they can be inhaled and can cause serious health problems according to the EPA.

As part of the settlement, Steel Dynamics has agreed to pay a civil penalty of $475,000 which will be split evenly between the state of Indiana and the U.S. government. The company will also upgrade the capture and control of emissions by building a new or expanded baghouse which will put the particulate matter emissions in compliance with the Clean Air Act.

EPA receives thousands of complaints about pet deaths, human injuries linked to flea collar
https://www.kiro7.com/news/trending/epa-receives-thousands-complaints-about-pet-deaths-human-injuries-linked-flea-collar/XC4TUZ6QYZHWZKBHSJF23RASY4/
By: Debbie Lord, Cox Media Group National Content Desk
Updated: March 2, 2021 - 10:24 AM

The Environmental Protection Agency has received thousands of complaints about a popular pet flea collar, including more than 1,600 incidents of pet deaths and 1,000 cases of harm to humans who have had contact with it, USA Today is reporting.

Seresto, a flea and tick collar, has been linked to the pet deaths and human injuries, according to EPA documents that show the agency has received more than 75,000 complaints in the past eight years.

The collar, designed to release small amounts of pesticide onto the animal for months at a time, is advertised as a flea and tick killer that is safe for cats and dogs.

"No pesticide is completely without harm, but EPA ensures that there are measures on the product label that reduce risk," an EPA spokesperson told USA Today in a statement.

"The product label is the law, and applicators must follow label directions. Some pets, however, like some humans, are more sensitive than others and may experience adverse symptoms after treatment."

According to the USA Today story, Bayer, the company that made the collars, did not respond to multiple requests for comment. To read the entire USA Today story, click here.

Groups Push Back on EPA's Effort to Neuter Asbestos Reporting Order
https://mesowatch.com/groups-push-back-on-epas-effort-to-neuter-asbestos-reporting-order/
By Cameron Ayers | Mar 2, 2021

States and anti-asbestos groups are pushing back on the Environmental Protection Agency's attempts to circumvent a court order mandating asbestos reporting requirements.

In legal briefs filed Feb. 26, three states and a coalition of anti-asbestos groups asked the Ninth U.S. Circuit Court of Appeals to enforce a Dec. 22 order compelling the EPA to include asbestos in its Chemical Data Reporting (CDR) requirements. Asbestos importers were previously required to report exposure and use data to the agency under the CDR, but the agency exempted asbestos from the requirements in 2017.

The court filings were prompted by a Feb. 2 agency request that the Ninth Circuit waive the order and the associated asbestos reporting rule. The agency proposed that in place of the order, it be allowed to simply revisit citizen petitions filed by the anti-asbestos groups to restore asbestos to the CDR reporting rules — petitions that the agency rejected, which prompted a lawsuit and the resulting court order.

Evasion Alleged
The anti-asbestos organizations — a coalition of six groups led by the Asbestos Disease Awareness Organization (ADAO) — accused the EPA of trying to evade its responsibilities with its latest legal maneuver.

"It has been two months since entry of the court's ... order and EPA has made no progress in amending the CDR rule," the brief states. "Instead of directing it to conduct rulemaking, EPA would convert the order into an open-ended remand that instructs EPA merely to reexamine the petition denials, without any obligation to propose amendments to the CDR rule or indeed take any action at all."

"Instead of directing it to conduct rulemaking, EPA would convert the order into an open-ended remand that instructs EPA merely to reexamine the petition denials, without any obligation to propose amendments to the CDR rule or indeed take any action at all." — Legal Brief

The filings asked the Ninth Circuit to reject the EPA's proposed revisions to the order and impose a compliance schedule for the agency to follow. The ADAO brief includes a suggested order that would require the agency to propose CDR amendments within 45 days and to finalize the proposals 60 days later. Such a compliance schedule is "realistic and achievable," the filing asserts.

States Chime In
A separate filing from three of the 10 states involved in the case — California, Massachusetts and Connecticut — echoed many of the arguments made in the ADAO brief, noting that the EPA's request was attempting to "litigate old matters" by offering nothing new in its defense.

It also contended that the EPA's motion failed to demonstrate that the court's order commits a "manifest error of law," the legal standard for amending a judgment.

In a statement, ADAO's counsel — Robert Sussman of the firm Sussman & Associates — said the group is "disappointed" that this was its first experience with the new administration under President Joe Biden, "especially since during the presidential campaign, Biden's team made it clear he was ready to address the horrible legacy of asbestos death and disease in our country."

Motion to Intervene
On a related note, a trade association for chlor-alkali producers — the Chlorine Institute — filed a motion to intervene in a connected case on Feb. 25. The motion was prompted by a Jan. 26 filing from ADAO asking the Ninth Circuit to review the EPA's handling of a risk evaluation for asbestos, which focused exclusively on chrysotile asbestos.

More specifically, the motion centered on ADAO's request that the court review the EPA's decision "determining the risks of certain conditions of use of chrysotile asbestos fibers but declining to consider the risks of other asbestos fibers, conditions of use, health effects and pathways of exposure that impact public health."

In the Chlorine Institute's eyes, this request was ambiguous, as the organization could not determine whether the request applied to chrysotile asbestos — which the group champions on behalf of its members — or only other forms of asbestos.

Uncertainty Abounds
Based on that uncertainty, the group filed its motion with the court, saying it should be allowed a seat at the table if ADAO seeks to restrict the importation or use of chrysotile.

"The Institute's member companies who use chrysotile asbestos for the manufacture of chlorine may be adversely affected by such remedies, depending on the precise remedies petitioners seek," the motion stated.

In a Feb. 28 release touting the Chlorine Institute's response, ADAO noted that it does indeed harbor concerns about the EPA's conclusions on chrysotile's risk, though the group did not explicitly say this was the intention behind its filing.

Report raises questions about popular flea collar
https://www.wzzm13.com/article/life/pets/report-raises-questions-about-popular-flea-collar/69-86cc9f6a-0086-4dec-8438-29e6ce933622
Author: 13 ON YOUR SIDE Staff
Published: 3:36 PM EST March 2, 2021
Updated: 3:36 PM EST March 2, 2021

The EPA has documented at least 1,698 deaths, and 75,000 incident reports related to the collars.

An investigative report published in USA Today is questioning the safety of one of the nation's most popular flea collars. The investigation, conducted by the Midwest Center for Investigative Reporting, reviewed thousands of complaints filed by pet owners with the Environmental Protection Agency.

The report links thousands of pet injuries and hundreds of deaths to the Seresto Flea Collar. It claims the EPA has documented at least 1,698 deaths, and 75,000 incident reports related to the collars.

13 ON YOUR SIDE reached out to Elanco, the company that makes the Seresto Flea Collar. A spokesperson provided us with a statement. "First, it is critically important to understand that a report is not an indication of cause.

What those numbers represent is the number of reports received, and do not reflect causality. The spokesperson goes on to say, "if a dog were to be wearing a collar and experience any sort of adverse event, the collar would be mentioned in the report." They say drawing a link between the two could be misleading.

Seresto collar was first introduced in 2012 and the company says it has protected 25-million dogs from fleas and ticks. Elanco says it does take any reports of adverse events seriously and does evaluate and report them to authorities if necessary.

The Midwest Center for Investigative Reporting says the chemical in the collar has also had an adverse affect on at least 1,000 people. Documents list ailments as rash, hives, numbness and headaches.

To read the complete article go Midwest Center for Investigative Reporting.

Steve Clark: It's wrong to say glyphosate is carcinogenic
https://madison.com/ct/opinion/mailbag/steve-clark-its-wrong-to-say-glyphosate-is-carcinogenic/article_d442f40c-2ea9-54ae-a8dc-4f08484c4f00.html
By Steve Clark
2 Mar. 2021

Dear Editor: A letter published Feb. 17 ("Does anyone in Madison care about pesticide use") was wrong to say that glyphosate (the herbicide in Roundup) is carcinogenic.

I began my science career at the EPA, working in pesticides the year Roundup came to market. The EPA found no problem with it then, and again found no problem in its recent update on glyphosate. In fact, no regulatory agency in the world has found glyphosate to be a problem. After my stint at the EPA, I became a medical school professor and expert in the blood cancers that glyphosate is alleged to cause. I confidently state that there is no credible science supporting the notion that glyphosate causes any cancer. In fact, the Agricultural Health Study, funded by the National Cancer Institute, included 45,000 pesticide applicators who handled glyphosate since 1993 found that there was NO association between glyphosate use and ANY cancer.

Readers might have seen advertisements from tort attorneys soliciting Roundup users for class action lawsuits against Monsanto, the manufacturer of Roundup. A couple of California juries found that glyphosate causes cancer. Their decisions were based on a report by the International Agency for Research on Cancer (IARC), an arm of the World Health Organization (WHO). The report declared glyphosate to be "probably carcinogenic." However, it later was revealed that the report ignored data that would have led the IARC to conclude that glyphosate is safe. The lead author admitted this to the Reuters News Agency. The WHO has disavowed the report.

Steve Clark
Madison

Popular flea collar linked to almost 1,700 pet deaths. The EPA has issued no warning.
https://www.usatoday.com/story/news/investigations/2021/03/02/seresto-dog-cat-collars-found-harm-pets-humans-epa-records-show/4574753001/

By Johnathan Hettinger
Midwest Center for Investigative Reporting
2 Mar. 2021

Rhonda Bomwell had never used a flea and tick collar before. Pierre, her 9-year-old Papillon service dog, was mostly an indoor animal.

Still, her veterinarian recommended she purchase one, so Bomwell went to the pet store near her home in Somerset, New Jersey, and selected Bayer's Seresto collar.

A day later, on June 2, 2020, Pierre had a seizure, collapsing while Bomwell was making dinner. Lying on his back, the dog stopped breathing and his eyes rolled back.

Bomwell tried giving him CPR. Then she called the police. An officer helped her lift the dog into her car, and she rushed him to the hospital. Pierre died before he could receive medical treatment. Bomwell didn't think to take off Pierre's collar.

"I just didn't put it together," she said.

Bomwell isn't alone. Seresto, one of the most popular flea and tick collars in the country, has been linked to hundreds of pet deaths, tens of thousands of injured animals and hundreds of harmed humans, U.S. Environmental Protection Agency documents show.

Yet the EPA has done nothing to inform the public of the risks.

Seresto, developed by Bayer and now sold by Elanco, works by releasing small amounts of pesticide onto the animal for months at a time. The pesticide is supposed to kill fleas, ticks and other pests but be safe for cats and dogs.

But thousands of pets are being harmed, according to federal documents obtained through a public records request from the Center for Biological Diversity, a nonprofit organization that watchdogs the EPA as part of its work to protect endangered species. The center provided the documents to the Midwest Center for Investigative Reporting.

Since Seresto flea and tick collars were introduced in 2012, the EPA has received incident reports of at least 1,698 related pet deaths. Overall, through June 2020, the agency has received more than 75,000 incident reports related to the collars, including nearly 1,000 involving human harm.

The EPA is in charge of regulating products that contain pesticides. The agency has known about these incidents for years but has not informed the public of the potential risks associated with this product, said Karen McCormack, a retired EPA employee who worked as both a scientist and communications officer.

McCormack said the collars have the most incidents of any pesticide pet product she's ever seen.

"The EPA appears to be turning a blind eye to this problem, and after seven years of an increasing number of incidents, they are telling the public that they are continuing to monitor the situation," she said. "But I think this is a significant problem that needs to be addressed sooner rather than later."

The EPA declined to say how Seresto compares to other pet products. But in response to a question about whether the product is safe, an agency spokesperson said in an emailed statement that the two pesticides in Seresto have "been found eligible for continued registration" based on best available science, including incident data.

"No pesticide is completely without harm, but EPA ensures that there are measures on the product label that reduce risk," the spokesperson said. "The product label is the law, and applicators must follow label directions. Some pets, however, like some humans, are more sensitive than others and may experience adverse symptoms after treatment."

Amazon, where Seresto is the top-selling collar, also has received numerous complaints about the product from customers who detailed significant issues. Dozens of people over the years have claimed the collar caused skin rashes in their pet. Others said it led to neurological issues in their pets.

Despite the many warnings, Amazon has not removed the product from its online marketplace. Amazon did not respond to multiple requests for comment for this story.

This isn't the first time that the EPA has failed to properly regulate flea and tick collars containing pesticides, said Miriam Rotkin-Ellman, a senior scientist at the Natural Resources Defense Council.

The NRDC filed a petition against the agency more than a decade ago over its approval of a different pesticide than the one used in Seresto that is linked to cancer and brain development issues in children.

In April 2020, a federal appeals court called the EPA's refusal to respond to NRDC's requests "nothing short of egregious" and told agency officials to make a decision on whether to ban the pesticide within 90 days. The EPA decided not to ban the pesticide, called tetrachlorvinphos. That pet collar continues to be sold under the brand name Hartz Ultraguard, Hartz InControl and Longlife.

NRDC has challenged that decision; that lawsuit is currently pending.

Even so, the number of incidents linked to that pesticide pales in comparison to those linked to Seresto. From 1992 to 2008, the EPA received about 4,600 incident reports regarding pet collars containing tetrachlorvinphos, including 363 deaths, according to EPA documents.

Broken down per year, that's 30 times fewer incidents and 10 times fewer deaths than Seresto.

And those are most likely an undercount, said Nathan Donley, a senior scientist at the Center for Biological Diversity and an expert on U.S. pesticide regulation. Donley said the number of reported incidents for Seresto is "just the tip of the iceberg."

In order to report an incident, a person has to make the connection between the collar and the issue with the dog, understand who to contact and how to report it, he said.

"Most of the time, people are not going to make the connection or they're not going to take an hour or so out of the day and figure out how to call and spend time on hold," Donley said.

He said the incident data creates lots of questions about EPA processes.

"My God, if this doesn't trigger a concern, that's a fundamental problem with the process," Donley said. "The fact that EPA has not done anything to alert the public that there might be an issue here, it strikes me as bordering on criminal. The EPA has this system in place to compile information and it's just collecting dust in some database."

A big business

Pet collars are big business. In its 2019 annual report, German agribusiness and pharmaceutical company Bayer reported revenue of more than $300 million on Seresto alone.

The company sold its animal health division to Elanco Animal Health, a former subsidiary of Eli Lilly and Co., for $7.6 billion in 2019. The deal was finalized in 2020. As part of the deal, Bayer received $2.3 billion in Elanco stock, which the company said it would sell over time.

Bayer did not respond to multiple requests for comment.

Since being spun off as its own company in 2019, Elanco has lobbied the EPA quarterly on issues relating to animal health, according to the the nonprofit Center for Responsive Politics, which maintains a website tracking political contributions. Over two years, the company has spent $1.6 million on lobbying, records show.

Keri McGrath, a spokeswoman for Elanco, said in an email the company "takes the safety of our products very seriously and thoroughly investigates potential concerns related to their use." McGrath pointed out that regulatory authorities have approved the product in more than 80 countries, and the EPA is in the final stages of re-approving both pesticides. There is no timeline on the final decision.

McGrath said that global data shows that 1 in 568 users of Seresto have an incident and "the majority of these incident reports relate to non-serious effects such as application site disorders, e.g. a reddening of the skin or hair loss below the collar."

"Keep in mind that the existence of an adverse event report does not necessarily mean the product caused the problem," she said. "Causality between the observed signs and the use of the product is evaluated on a case-by-case basis. That said, every adverse event collected, regardless of causality, is reported to the authorities."

The EPA did not respond to a request about how Seresto compared to other flea and tick collars in terms of incidents. The Midwest Center has filed a Freedom of Information request for the incident database, but that request has not yet been filled.

The extent of the damage is uncommon, said McCormack, the former EPA staffer.

"I've never seen any product that had 75,000 incidents," McCormack said.

Seresto's pesticides more toxic together

The EPA approved Seresto collars on March 16, 2012. The collars are designed to work for eight months.

Under the Federal Insecticide, Fungicide and Rodenticide Act, the EPA must determine a pesticide product will not cause "unreasonable effects on the environment."

This determination requires weighing harms versus benefits, including assessments of risks to human health and the environment.

Seresto contains two pesticides: imidacloprid and flumethrin.

Imidacloprid belongs to the neonicotinoid class of insecticides, which are the most commonly used insecticides on crops in the U.S. Despite neonicotinoids being connected to massive die-offs of non-target insects such as bees and butterflies, the EPA proposed re-approving imidacloprid and other class members last year. The pesticide is banned in the European Union for outdoor use but allowed in pet collars. There is also growing evidence that mammals can be harmed by these pesticides as well.

Flumethrin, EPA documents show, is only an active ingredient in one product: Seresto.

Like with most pesticides, the data supporting the registration of Seresto was conducted by the company that produced it, Bayer. The majority of the studies were looking at each pesticide individually.

However, a 2012 Bayer study found they have a "synergistic effect," meaning they are more toxic together on fleas. The study found that the "unique pharmacological synergism" works as quickly as six hours to prevent ticks from attaching and feeding, preventing disease transmission.

Additionally, eight companion animal safety studies were conducted by Bayer looking at the effect of Seresto collars on domestic cats and dogs. The EPA used these studies to approve Seresto. The California Department of Pesticide Regulation took issue with the validity of two of the studies but approved the collars anyway.

Another issue could be a reaction of inactive ingredients, which are unknown and have caused problems in spot-on treatments, said Donley of the Center for Biological Diversity.

Donley, who has a doctorate in cell and developmental biology and is a former cancer researcher, said this "synergistic effect" likely extends to pets. He said he wasn't sure what makes the two pesticides so likely to cause harm, but it is clear something is wrong with the product.

"You don't even see these kinds of numbers with many agricultural chemicals," Donley said.

"For whatever reason, this combination is just really nasty."

History of unsafe pet treatments

There are currently 18 flea and tick collars on the market: three that are approved for both dogs and cats (including Seresto), 10 approved for dogs and five for cats, according to the National Pesticide Information Center.

In addition to allowing tetrachlorvinphos in pet collars despite evidence of its safety issues, the EPA also had approved the use of another pesticide linked to cancer and brain development problems – propoxur, which was sold under many brand names, including Bio Spot, Scratex Color, Zodiac, Sergeant's Dual Action and Sentry Dual Action.

Rotkin-Ellman's research showed residues were high enough to pose a risk to children and adults who play with pets that were wearing the collars.

In April 2016, pesticide companies voluntarily agreed to stop using propoxur to help protect children's health. The brand names that used propoxur have switched to other active ingredients.

In addition, in 2010, the EPA increased label requirements and limited some inert ingredients in spot-on treatments, which are applied to a specific area of a pet. This happened after incident data showed the treatments were causing hundreds of pet deaths, as well as issues such as irritation, rashes and hair loss, gastrointestinal problems and seizures.

Collars have caused seizures, rashes in humans
It's not just pets that are being harmed, EPA documents show.

Between 2013 and 2018, 907 incidents were reported with humans, according to a September 2019 EPA assessment of human health risk.

The assessment determined that there were 19 severe incidents. Of those, eight people had dermal symptoms, such as a rash or hives, and seven had neurological symptoms, which included numbness and headaches.

Incidents listed by the EPA included:
A 12-year-old boy who slept in a bed with a dog wearing a collar started having seizures and vomiting. He had to be hospitalized.
A 67-year-old woman who slept in a bed with a dog wearing a collar reported having heart arrhythmia and fatigue.
A 43-year-old man put collars on eight dogs and slept in the same bed as four of the dogs. A week later, he developed ear drainage and nasal and throat irritation and was told by a doctor that he had a hole in his ear drum. He removed the dog collars and the symptoms went away. He later reapplied the collars and the symptoms returned.

An October 2016 EPA bulletin responded to citizen concerns about children being exposed to Seresto, saying it had found exposure to the collars to be negligible.

"As stated in the precautions on the label, do not allow children to play with the collars. In addition, try to keep the pet away from young children for a day after putting on the collar to minimize exposure," the bulletin said.

"It's really not just happening to animals. It's happening to people who pet them as well," Donley said. "I have two young kids who are all over our dog all the time. I can imagine how highly exposed people would be to residues."

'It's just been a nightmare'
To Bomwell, the worst part was the lack of warning. Pierre had never been sick or had a seizure. He was just 9, so she thought he had half a decade left. Her last dog had died at 18. Plus, she felt like she was responsible. She was the one who put the collar on.

"It was so bizarre," Bomwell said. "It's just been a nightmare."

Even if the EPA had not received tens of thousands of complaints, a cursory search of the web would find dozens of posts from pet owners warning others to be careful with the collars, including a letter to an animal doctor column in the St. Louis Post-Dispatch in 2013, a radio news story in New York in 2016 and extensive comments on pet forums.

Without the federal government stepping in, individuals are left in the dark. That's something Ron Packard, of Brockton, Massachusetts, is hoping to address.

In the days after the death of his two dogs in June 2019, Packard did what any person looking for answers does: He went to the internet.

Two of Packard's four dogs had recently had seizures on the same day, before becoming lethargic and vomiting and finally, refusing to eat. He brought them to the veterinarian, who couldn't find a problem.

Within weeks, the two previously healthy cavachons, 10-year-old Danny and 5-year-old Dominic, were both dead.

The only thing Packard could figure out was both dogs had started wearing Seresto flea and tick collars a month before.

"Thirty-three and 54 days later, they're both dead," Packard said.

Packard created a Facebook page, asking people who had similar issues to share their stories.

Today, the page fills up with pictures and stories like Packard's.

A dog starts wearing a collar. Within weeks, a dog will have a seizure, sometimes it will later die. Other stories aren't quite as extreme. Loss of hair around the neck. Lethargy.

Packard encourages everyone to report their story to the EPA.

"I don't want others to go through what we went through," he said. "Every time I read the stories, it brings me back to my dogs. But if I can save a few pets, I can deal with it."

This story is a collaboration between USA TODAY and the Midwest Center for Investigative Reporting. The center is an independent, nonprofit newsroom covering agribusiness, Big Ag and related issues. USA TODAY is funding a fellowship at the center for expanded coverage of agribusiness and its impact on communities.

Popular flea collar for pets linked to nearly 1,700 deaths, documents show
https://whdh.com/news/popular-flea-collar-for-pets-linked-to-nearly-1700-deaths-documents-show/
Frank O'Laughlin

(WHDH) — A popular flea and tick collar for dogs and cats has been linked to nearly 1,700 pet deaths, as well as tens of thousands of injuries, documents show.

Scores of pets are being harmed by Seresto collars, which work by releasing small amounts of pesticide onto the animal for months at a time, according to a new report published by the Midwest Center for Investigative Reporting and USA Today.

Since Seresto introduced the collars in 2012, the U.S. Environmental Protection Agency has received reports of at least 1,698 pet-related deaths. As of June 2020, the EPA had also received more than 75,000 incident reports related to the collars, according to documents obtained by the Center for Biological Diversity and shared with the Midwest Center for Investigative Reporting.

Nearly 1,000 of the reported incidents involved human harm, the documents indicated.

The EPA has known about the incidents for years but has not informed the public of the potential risk associated with the collars, according to Karen McCormack, a retired EPA official.

"The EPA appears to be turning a blind eye to this problem, and after seven years of an increasing number of incidents, they are telling the public that they are continuing to monitor the situation," McCormack said in the report. "But I think this is a significant problem that needs to be addressed sooner rather than later."

While the EPA reportedly declined to say how Seresto compares to other pet products, an agency spokesperson said in an email to the authors of the report, "No pesticide is completely without harm, but EPA ensures that there are measures on the product label that reduce risk."

New Jersey native Rhonda Bomwell lost her Papillon service dog to a seizure in June, just one day after putting a Seresto collar on the animal, according to the report.

Seresto also remains the top-selling collar on Amazon, despite numerous complaints, the report points out.

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Why my polluted blood is boiling and yours should be too
https://theaggie.org/2021/03/02/why-my-polluted-blood-is-boiling-and-yours-should-be-too/
BY JOE SWEENEY — JMSWEENEY@UCDAVIS.EDU
2 Mar. 2021

It's time for the Biden Administration to protect the American people from "forever chemicals," forever

Teflon. An invention as American as apple pie, it has been used in everything from coating pipes in the Manhattan Project to everyday use in kitchens to coat non-stick pans. Teflon was so popular that in the 1980s that former president Ronald Reagan was affectionately nicknamed "The Teflon President," because no scandals ever seemed to stick to him. Teflon's "non-stick" ability was attributable to a surfactant called Perfluorooctanoic Acid (PFOA), which was only fully phased out of use by Dupont in 2014.

Today, it is common knowledge that PFOA has been linked to a vast amount of human health impacts, including kidney, testicular, liver and pancreatic cancer. Recent studies have also indicated that it is found in nearly every living thing on Earth, even in the most remote locations. You're probably wondering: How is this even possible? How did this harmful chemical go undetected for so long?

The easy answer is it didn't. Dupont, the company who makes Teflon, knew that PFOAs had potentially severe health impacts from their own study on dogs and rabbits, by 1961. Over the next few decades, 3M Company and Dupont did a series of internal studies, which linked PFOAs to birth defects, testicular cancer, pancreatic cancer and liver tumors in various species. Ultimately though, Dupont argued that they had no reason to believe that there were any adverse human impacts. This was fairly convenient considering they knew that there were high concentrations of the chemical in the blood of their workers at the Washington Works Plant since 1984. In fact, between 1951 and 2003, 1.7 million pounds of PFOAs were released into the environment around the plant meaning that the surrounding community was also likely impacted. The bottom line is that Dupont knew that PFOAs were likely dangerous just 10 years after they began using them, yet never informed the federal government or the Environmental Protection Agency (EPA).

It is likely that PFOAs toxicity might've gone undetected to the present if it hadn't been for a persistent farmer named Wilbur Tennant. In the late 1990s, Tennant, whose cattle had been dying mysteriously, blamed Dupont's new landfill which had opened adjacent to his land. Unable to find legal help within Parkersburg, Tennant resorted to reaching out to Robert Bilott, a corporate chemical defense lawyer whose grandmother lived in Parkersburg. Ultimately, Bilott was able to win a settlement for the Tennants, but was unsatisfied with the outcome as it allowed Dupont to continue to pollute the local community.

Bilott, among others, went on to sue Dupont in a class action lawsuit which Dupont settled on the basis that an independent science board would look into the toxicity of the chemical. With 70,000 participants involved in one of the largest epidemiological studies in history, the board took 7 years and concluded that there was a probable link between PFOA and a plethora of cancers. In response to this, Dupont rejected the evidence from the independent review and tried to fight every individual lawsuit on a person-to-person case. Many of the plaintiffs were terminally ill, and it was likely that Dupont was banking on the fact that many people would die or give up before getting a verdict. After several individual cases (and losses), the company settled with the entire class for $670 million dollars, less than what the company makes on Teflon in a single year.

To this day, the EPA has only marked PFOAs as a "chemical of concern," and cannot enforce any guidelines or health suggestions set by their review of the chemical. Bilott's battle with PFOAs illustrate the greater problem with the EPA's review process for unregulated chemicals. The loophole which allowed Dupont and 3M to

continue to pollute the entire country for decades essentially relied on self regulation which has historically never worked.

Additionally, PFOAs are only one of many chemicals that fall under the category of "forever chemicals," named for their persistence in both the environment and the human body. There are dozens of other chemicals that fall under this category, mostly unregulated, that must be a priority for the Biden administration's EPA. Despite increasing public outcry, change is slow. It's not a good sign that President Joe Biden's EPA transition team included an ex-Dupont consultant, but there have been significant strides towards increased regulation.

"I am cautiously optimistic that, with increasing public awareness of the global PFA [PFOAs] "Forever Chemicals" public health threat, we may finally see significant steps taken at the national level to effectively address the issue and to make sure that those who actually caused this problem are held responsible," remarked Bilott earlier this month over email.

If you are interested in learning more about PFOAs, Bilott's novel "Exposure" chronicles his decades long legal battle around the chemical or you can see the film "Dark Waters" starring actor Mark Ruffalo. Want to know more about forever chemicals or what's in your water? Check out the Environmental Working Group's Tap Water Database. It is essential for the health of our communities that the Biden Administration implements strong regulations around the production and use of "forever chemicals," like PFOA.

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Disclaimer: The views and opinions expressed by individual columnists belong to the columnists alone and do not necessarily indicate the views and opinions held by The California Aggie.

Sweeping climate bill aims for zero carbon emissions by 2050
https://www.rollcall.com/2021/03/02/sweeping-climate-bill-aims-for-zero-carbon-emissions-by-2050/
By Benjamin J. Hulac
Posted March 2, 2021 at 4:39pm

'Time for small marginal change is long past,' Pallone said of the bill that touches all corners of the economy

High-ranking House Democrats unveiled legislation Tuesday to zero out domestic greenhouse gas emissions by 2050, including deep cuts in the next decade, a deadline that has support from the world's leading climate scientists.

The draft bill would set a U.S. goal to reduce greenhouse emissions by at least 50 percent, from 2005 levels, by 2030. It would also set a national goal to "achieve net-zero" emissions by mid-century and direct heads of federal agencies to come up with plans for how to meet those targets by 2050.

"We have to act decisively," Rep. Frank Pallone Jr., D-N.J., chairman of the Energy and Commerce Committee, told reporters. "The time for small marginal change is long past. If we don't take meaningful nationwide action now our children will inherit an economy and a world beyond their capacity to repair."

In the Senate, Majority Leader Charles E. Schumer, D-N.Y., used similar language on Feb. 3 to describe climate change, calling it "the existential threat of our time."

Reps. Paul Tonko, D-N.Y., and Bobby L. Rush, D-Ill., the chairmen of the panel's subcommittees on the environment and energy respectively, said there would be hearings on the bill. While the committee members said they aim to move the bill through the committee process and gain Republican support, they did not rule out using the budget reconciliation process to advance it.

'Blueprint'
"It's a plan, it's a blueprint for bringing America back into stronger leadership," Tonko said.

The legislation is the first expansive climate bill either party has offered this Congress, which has seen Democrats make climate change an early priority on Capitol Hill and in the White House. Congressional Republicans have decried President Joe Biden's steps to rein in emissions.

While China emits the most greenhouse gases of any nation now, the U.S. remains the No. 1 historical emitter.

The legislation, which would authorize $565 billion over 10 years, is more aggressive than a previous version of the bill introduced in January 2020.

Broad in scope, the new legislation covers the power, transportation, industry and manufacturing sectors, as well as environmental justice, waste reduction and financial topics.

Clean electricity
It would establish a clean electricity standard to require utility companies to generate an increasing percentage of their electricity from zero-emissions sources. The standard would reach 80 percent by 2030 and 100 percent by 2035.

Senate Democrats are expected to introduce a clean electricity standard as part of an infrastructure bill that could be the next major legislative proposal after Congress finishes work on the $1.9 trillion pandemic relief bill.

Asked about pricing carbon emissions through a tax or a cap-and-trade market, Pallone said that was not his preferred method of lowering heat-trapping gases.

"I think it's time to try something new," said Pallone. "The votes are just not there for a price on carbon."

The 981-page bill is more ambitious than the version on display last Congress in part because it would set an interim goal of cutting emissions 50 percent by 2030.

Scientists with the United Nations' Intergovernmental Panel on Climate Change, or IPCC, the leading international voice on climate, warned in a landmark 2018 report that international leaders have until 2030 to get emissions under control and halt temperatures from rising more than 1.5 degrees Celsius beyond pre-industrial levels — the threshold past which scientists say climate change gets significantly worse.

Tonko said the House committee listened to input from Biden and Vice President Kamala Harris, adding that the "[clean energy standard] is something that they believe in."

Support for standard
Lindsey Walter, deputy director for the climate and energy program at Third Way, a centrist think tank, said by phone the legislative structure of the Biden administration's climate goals are starting to emerge.

"I think it's perhaps the best policy we have in play right now to decarbonize the electricity sector," Walter said of the CES concept. "There's a lot of support behind a clean energy standard."

She said, "We're beginning to see actual legislative language being put together to enact the Biden legislative agenda."

The bill includes ten sections and hundreds of policy proposals and line items, including $2.5 billion for a "clean school bus" program at the EPA and would authorize $2.5 billion annually to increase the pace of transitioning petroleum-powered buses to zero-emissions buses, according to a summary.

It would also set a 10-year deadline for the cleanup of all federal Superfund sites vulnerable to climate change.

Phillies Announce an 8,800-Fan Capacity for First 19 Games
https://www.sportstalkphilly.com/2021/03/phillies-announce-an-8800-fan-capacity-for-first-19-games.html
03/02/2021

The news is good for Phillies fans who hope to attend games at Citizens Bank Park. As the State of Pennsylvania increased capacity at outdoor events to 20%, the Phillies were able to make more firm fans for the opening of the 2021 MLB Season at Citizens Bank Park. The Phillies announced on Tuesday that 8,800 fans may be in attendance for games.

The Phillies announced the following measures beyond the 8,800 fan capacity:

- To allow for socially distant seating, fans will be seated in pods of two, three or four people, with limited pods available for five to six people.
- All attendees age two years and older must wear a face covering over their nose and mouth at all times on ballpark property, other than when actively eating or drinking at their ticketed seats.
- All areas of the ballpark accessed by fans will be cleaned and disinfected before, during and after each game by a newly created "Clean Team" utilizing processes and products approved by the CDC and EPA specifically for use against COVID-19. Hand sanitizing stations will also be widely available.

Tickets for the first 19 games will be first offered to Season Ticket holders. The remaining tickets will be put on sale on March 12. In April, as the COVID atmosphere is a little bit clearer, they will sell games beyond the first 19 games.

The Phillies note that the tickets available could increase or decrease depending upon health protocols at that time.

EPA awards contracts to clean abandoned uranium mines on the Navajo Nation
https://www.nhonews.com/news/2021/mar/02/epa-awards-contracts-clean-abandoned-uranium-mines/
By Stan Bindell, for the Navajo-Hopi Observer
Originally Published: March 2, 2021 9:33 a.m.

FLAGSTAFF, Ariz. — The U.S. Environmental Protection Agency (EPA) announced Feb. 11 three contract awards for cleanup efforts at more than 50 abandoned uranium mine sites on and around the Navajo Nation, including at least 10 sites in Arizona and others in New Mexico.

The Navajo Area Abandoned Mine Remedial Construction and Services Contracts (AMRCS), worth up to $220 million over the next five years, were awarded to Red Rock Remediation Joint Venture, Environmental Quality Management Inc. and Arrowhead Contracting Inc.
Margot Perez-Sullivan, a spokeswoman for the EPA in San Francisco, said uranium remediation projects will take place in 10 Navajo Nation Chapters: Tolikan (Sweetwater), Round Rock, Lukachukai, Casamero Lake, Standing Rock, Teec Nos Pos,, Cove and Coyote Canyon.

U.S. Rep. Tom O'Halleran (D-AZ), said the money could clean up as many as 200 of the 500 uranium mines on the Navajo reservation that need remediation. However, O'Halleran said, with inflation, the funds may not be quite enough to remediate as many as the hoped for 200 uranium mines.

O'Halleran said there is a tremendous amount of work to do on the 500 uranium mines that are considered unsafe.

"I've seen some of those mines myself that are in terrible condition," he said.

O'Halleran said the clay surrounding the mines often crack in the sun allowing contamination to run down into washes or streams.

"The Navajo Nation is full of stories about families decimated by cancer," he said.

O'Halleran said some jobs from this project will go to tribal members.

"We worked hard to get this accomplished over time. We will make sure to get more funding," he said. "The EPA will be more active in protecting Navajo people and the Grand Canyon."

O'Halleran said it is important that the EPA respect tribal sovereignty.

"It's a plus because we want to make sure that we have the necessary money and have tribal input," he said. "We don't want the feds coming in and saying: 'We're going to do this' like they have in the past."

O'Halleran said he is concerned about the ongoing contamination of rivers and streams by uranium mines.

"We've talked about this until we're blue in the face. When we first came to Congress, nobody understood this and now they do. They know that this is life threatening. We know that children are playing in them because not all of these areas are fenced," O'Halleran said.

While he doesn't know anyone in Congress who opposes the remediation of the uranium mines, O'Halleran said it is always a question of where the funding is placed on the priority scale.

"If this was across from the (U.S.) Capitol, we wouldn't have waited 80 years for the cleanup," he said.

Deborah Jordan, acting regional administrator for the EPA's Pacific Southwest office, said in a news release that the EPA continues to work with the Navajo Nation EPA and local communities to address the legacy of abandoned uranium mines.

"These contract awards mark a significant step in this ongoing work," she said.

Most of the funding for the contracts comes from the nearly $1 billion settlement reached in 2015 for the cleanup of more than 50 abandoned uranium mine sites for which Kerr McGee Corporation and its successor, Tronox, have responsibility.

In addition to the funds from that Tronox settlement, EPA and the Navajo Nation have secured funding agreements, through enforcement agreements and other legal settlements, for the assessment and cleanup of approximately 200 abandoned uranium mine sites on the Navajo Nation.

Work is slated to begin later this year following the completion of assessments in coordination with Navajo Nation's environmental agency, the Navajo Nation EPA.

The Navajo Nation EPA has not returned calls seeking comment.

Letters: RMG chief: The metal recycling facility on the Southeast Side will not be another General Iron
https://www.chicagotribune.com/opinion/letters/ct-letters-vp-030321-20210302-2uxaumynl5ca5aiupmor6opi4u-story.html
CHICAGO TRIBUNE |
MAR 02, 2021 AT 3:17 PM

Like the activists who are on a hunger strike trying to block Chicago from issuing a permit, the editorial "The Southeast Side should not be the city's ashcan" (Feb. 24) fell victim to the temptations of false equivalence.

My company, Reserve Management Group, owns Southside Recycling, a new business in the final stages of constructing a metal recycling operation on land that RMG has owned for more than 20 years. This facility will set a new standard for environmental protection among U.S. metal shredders.

Some of the equipment that will be installed at Southside Recycling was used at General Iron. But there are stark differences between the two locations.

General Iron operated on 10 acres in Lincoln Park. Public streets ran within feet of equipment and material. Southside Recycling sits on 25 acres within a 175-acre site where RMG has operated other recycling businesses for decades without community objection. It provides ample separation from our neighbors. Expanding recycling on our revitalized brownfield actually serves the environmentalists' goal of advancing a "Green Economic Industrial Corridor."
SEE MORE
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Opponents have invoked environmental scandals entirely unconnected to RMG in a bid to paint us as a wanton polluter. The harms done to the area by petcoke and manganese operations are tragic, but our recycling facility will not handle such materials. Attempts to associate us, and metal recycling, with such wrongdoing are exceedingly disingenuous.
Due process and the rule of law require that our permit should be granted. After more than a year of public comment periods on multiple permit applications and the city Public Health Department's new rules for large recycling facilities, our project has stood up to every challenge.

The U.S. Environmental Protection Agency is attempting to informally resolve a civil rights complaint with the Illinois EPA. However, the federal EPA made clear that its inquiry does not in any way affect our construction permit properly issued by the state EPA.

Residents may disagree on the appropriateness of rules, but there is no denying that our city permit application meets or exceeds the regulations. Opponents' rejection of recycling's environmental and economic benefits aside, the irrefutable compliance of our application alone speaks loudly in favor of granting the permit.

— Steve Joseph, CEO, Reserve Management Group, Chicago

Zoning rules and pollution

That the General Iron (Reserve Management Group) project was able to get close to approval before a serious reckoning with the pollution burdens borne by Southeast Side residents is sobering proof of the systemic environmental injustice that plague Chicago. In this case, it falls on neighborhoods bordering Lake Michigan and the 6-mile Calumet River.

Chicago can choose a different path now, and respect the health and environment of everyone who lives here. The Alliance for the Great Lakes recently released research after two years of work with partners including leaders in the fight against General Iron like the Southeast Environmental Task Force, Southeast Side Coalition to Ban Petcoke and the Southeast Youth Alliance. The evidence is clear: The health and environmental futures of Chicagoans are at risk from decades of industrial overdevelopment and under-regulation of pollution. In the Calumet industrial corridor — where Hispanic/Latino and Black residents make up about 59% and 25% of that area's population, respectively — rates of heart disease and pulmonary disease are higher than the rest of Chicago. Many residents remain "medically underserved," facing shortages of primary health care services.

Our data shows a root cause of the location of pollution: the impacts of Chicago's zoning regulations, which have been concentrating pollution sources in Black and brown communities over the last three decades. City leaders and federal agencies like Housing and Urban Development must continue investigations of how rezoning plans for the North Branch resulted in the General Iron move to the overburdened Southeast Side.

But we can't stop there. Southeast Side communities also aren't able to enjoy safe and healthy access to Chicago's great waters like the Calumet River. These problems are not new, but they merit every ounce of attention they get. To confront generational injustices, the city needs to work directly with residents to craft zoning reforms that prioritize public health and true sustainability when planning for the next uses of our precious river corridors and lakefront.

The alliance stands with the Southeast Siders demanding an end to land-use policies that perpetuate environmental racism. Stricter regulations, stronger enforcement and the use of community-generated data in making decisions are key pieces of a vision that will support the environmental, personal and economic health of people in Chicago's unique waterfront communities.

— Joel Brammeier and Olga Bautista, Alliance for the Great Lakes, Chicago

Join the conversation in our Letters to the Editor Facebook group.
Submit a letter, of no more than 400 words, to the editor here or email letters@chicagotribune.com.

Sen. Mark Kelly says he's in a position to help Native Americans
https://www.nhonews.com/news/2021/mar/02/sen-mark-kelly-says-hes-position-help-native-ameri/
By Stan Bindell, for the Navajo-Hopi Observer
Originally Published: March 2, 2021 10:08 a.m.

PHOENIX — U.S. Sen. Mark Kelly has received his committee assignments and said he will be in a position to help Native Americans on many issues such as veteran's affairs, the environment and the elderly.

Kelly, D-Ariz., has been assigned to the Armed Services Committee, Energy and Natural Resources Committee, Environment and Public Works Committee, Special Committee on Aging and the Joint Economic Committee.

Kelly put the Armed Services Committee at the top of his list as he is a 25-year Navy veteran who served as a combat pilot and astronaut.

"From Ira Hayes, to Lori Piestewa, to the Navajo Code Talkers, Arizona tribal members have sacrificed for their country with honor and distinction," he said. "As a veteran of the U.S. Navy, I have served alongside Native servicemen during my career in the Navy and I am committed to ensuring that Native Americans receive all respect, rights and benefits entitled to them during and after their service."

Kelly said he supports expanding veterans programs to ensure service reaches all tribal nations. He said rural tribes are often the most underserved with issues such as health care, homelessness, social services and national cemetery access often overlooked by the federal government.

"I believe that more field support from the VA (Veteran's Affairs) in rural areas is needed, along with a large scale expansion of broadband internet across tribal communities to increase veteran access to telehealth and remote learning programs," he said.

Kelly said it is also important for America to honor Native veterans and celebrate the legacy of Navajo Code Talkers. He supports the efforts by the Navajo Nation to establish a Navajo Code Talkers Memorial.

"Too often the Indian Health Service and the Veterans Affairs system are underfunded by Congress and unable to provide the full range of health care and veteran benefits that tribal members deserve. In the Senate, I am currently advocating for resources for tribal governments, health care, water systems and housing in this year's COVID-19 assistance package," he said.

By serving on the Energy and Natural Resources Committee, Kelly said the federal government should play a role in helping the Navajo and Hopi transition to a renewable energy economy following the closure of the coal fired Navajo Generating Station and the Kayenta Coal Mine. Kelly said the Navajo and Hopi tribes have significant solar and wind potential, which they should be encouraged to grow.

"In my new role on the Committee on Energy and Natural Resources and the Committee on Environment and Public Works, I plan to push for renewable energy programs, mining remediation projects and climate policies that benefit tribes," he said.

From his seat on the Environmental and Public Works Committee, Kelly recently supported the advancement of Michael Regan's nomination for Administrator of the EPA.

"I spoke about the fact that the EPA should prioritize the cleanup of the roughly 500 abandoned uranium mines in the Four Corners region. And I will continue to use my seat on the EPW Committee to ensure that tribes enjoy clean water, air, and land," he said.

Kelly said he will use his seat on the Aging Committee to help with elderly issues for Navajo, Hopi and other tribes.

"The COVID pandemic has highlighted in our country just how underserved Native elders are when they seek adequate health care and other social services," he said. "I am committed to continue working with tribal communities in Arizona on ways to best help aging Native populations. I will work with Chair Casey and Ranking Member Scott on the Senate Aging Committee to make sure our committee hearings, reports and oversight include the unique needs of tribes."

$48 million Blacksnake Creek project nearing completion
https://www.newspressnow.com/news/local_news/48-million-blacksnake-creek-project-nearing-completion/article_0d2e7f76-7b7f-11eb-b9c4-0b192ba45222.html
By Quinn Ritzdorf News-Press NOW
2 Mar. 2021

After seven years and nearly $50 million spent, the Blacksnake Creek Stormwater Separation Improvement project is almost complete.

The final stage is to make improvements to the sewer outfall discharge channel, which became more complicated after the Missouri River flooded in 2019. This ultimately delayed the project for more than a year.

"The only part remaining is the delivery of the new gate that shuts that off when the river's high," said Andy Clements, St. Joseph's director of public works and transportation. "That should be in maybe April or May. When that's in, that will be complete. So (it's) pretty much all done, just kind of the final dotting the i's and crossing the t's."

St. Joseph was mandated by the Missouri Department of Natural Resources and the United States Environmental Protection Agency to address the overflow at the water treatment plant due to rising levels of creeks and streams.

"We always have been treating all the water that runs through our streams, and all the water has been running through our sewer plants, our treatment plants," said City Councilman Kent O'Dell. "By separating them, it stops the possibility of having these overflows where the sewage plant gets overwhelmed and actually starts dumping back into the river."

Cities along many major rivers, like the Missouri, suffer from this problem, and St. Joseph isn't the only one to be mandated by these agencies.

"Any city that's on the rivers, no matter what river it is, is just getting hammered on these mandates by EPA," O'Dell said. "We've just gotten beat to death and we're so much further than everybody else on getting these mandates accomplished."

The entire project cost about $48.6 million, which the city paid a majority of with bond proceeds. That price tag was the reason the project took so long.

"This Blacksnake Creek project isn't something that we had the money or the ability to do overnight," said City Councilman Brian Myers. "All the changes that we have to make involving dumping untreated sewage into the river, it's costly. We're under a mandate by the Missouri Department of Natural Resources, so we don't have a choice."

Blacksnake has been operational since July, but the final installation of the gate this spring will officially complete the long project. The Missouri Department of Natural Resources and the EPA will monitor the process and make sure it meets their regulations.

"It's been a long project," Clements said. "I'm glad to get it done and move on."

Did Trump Really Make Dishwashers Great Again?
https://www.nytimes.com/wirecutter/blog/dishwashers-trump-efficiency/
PUBLISHED MARCH 2, 2021
Liam McCabe

In October 2020, the Trump administration passed a new rule for dishwasher efficiency, claiming that it would undo "burdensome regulations" that made dishwashers slow and weak, and that it would "allow Americans to wash dishes in under an hour!" Donald Trump himself even boasted on the campaign trail: "Now you can buy a dishwasher and it comes out beautiful."

Trump was right: Today, you can buy an affordable dishwasher that does an excellent job in an hour. (We recommend several in our guide to the best dishwashers.)

But that was true even before the new rule.

Any dishwasher that you can buy today is regulated under the same "burdensome" efficiency guidelines that have been in place since 2013. And some companies still found a way to make fast, effective, and efficient machines. Trump promised to make dishwashers great again, but it turns out they were great all along.

How dishwasher efficiency (barely) changed under Trump

The Trump administration did indeed tweak the existing rules for dishwasher efficiency—a little. The Department of Energy created a new product class (PDF): fast dishwashers, defined as dishwashers that can wash and dry a load of dishes in an hour or less on their default setting. (If you're keeping score, this is actually a new regulation, not deregulation.)

Fast dishwashers are not subject to the same water- and energy-efficiency standards as conventional dishwashers because they're actually a different type of product in the eyes of the DOE. Though some environmental-advocacy groups have asserted that fast dishwashers will be exempt from any efficiency rules, the DOE confirmed with us in an email that there will be regulations—they just haven't been made yet, because that's a separate years-long process from the initial years-long process of deciding to create the new product class.

Here's a fun fact: The US government has never restricted the amount of water or energy that your dishwasher can use, except for the "normal" cycle. As long as that "normal" cycle meets the benchmarks for water and energy use on a standardized test (no more than 5 gallons of water per load and 307 kWh of energy per year with average use), the dishwasher can be sold in the US. Most people use their machine's "normal" cycle most of the time, so this rule alone conserves a lot of resources.

But no other dishwasher cycles are governed by the DOE, according to an agency spokesperson. So "heavy" or "quick" or "sensor" or any other setting that isn't defined as the "normal" cycle can use as much water or energy as the dishwasher maker likes.

Note that Energy Star is a different and completely voluntary efficiency program administered by the Environmental Protection Agency—not the Department of Energy. It limits water use for the "normal" cycle at 3.5 gallons per load and energy use at 270 kWh per year. Even though it's optional, nearly all dishwasher models sold as of early 2021 meet the Energy Star standards, including almost all of the models that already have a one-hour wash cycle. (The Trump administration did not make any changes to the Energy Star program for dishwashers.)

Most dishwashers already clean well, and some are already fast

We tested 17 popular dishwashers (the results of which we'll publish soon in our updated guide), and they all performed well on our cleaning tests on their "normal" cycles (though sometimes we had to use a higher-end detergent to get great results). We also scoured more than a thousand customer reviews for another 10 models and found very few complaints about cleaning performance at all, except for one particularly old and cheap model.

Nearly all of these models (and most dishwashers in general) have a fast-wash cycle, some of which are already as quick as 34 minutes. Usually, though, the cycle takes about an hour, especially if the dishwasher also tries to dry the dishes. Some fast cycles did perform pretty poorly in our rigorous-cleaning test, which involved a lot of stubborn, baked-on soils. The Competitive Enterprise Institute, a think tank that petitioned the DOE to create the new fast dishwasher class, correctly points out that most manufacturers recommend their machines' fast cycles only for lightly soiled loads. So the drop in performance makes sense.

But a few other brands (including Bosch, Whirlpool, and Miele) say that it's fine to use their models' fast cycles for standard loads of dishes (as long as the dishes aren't too crusty). We tested some of these models, and we often got great results—even with burnt-on soils.

These quick, effective performers weren't particularly profligate with water and energy, either. For example, Bosch's Speed60 cycle (found in some dishwashers that have been as cheap as $500 on sale) cleaned better than the "normal" cycle on some other models (including certain pricier ones). And the Speed60 mode still used just 3.8 gallons of water per cycle—more than the "normal" cycle (usually) and a bit too much for Energy Star, but well under the 5-gallon DOE limit. It also used nearly the same wash and rinse temperatures as a "normal" cycle would, so the energy use was similar, if not slightly lower because of the shorter wash time.

If your dishwasher sucks, blame the brand

Regulations for water and energy efficiency in dishwashers have been steadily tightening since the early 1990s. Sachin Sood, a former Bosch product manager, told us that it's fair to say that those restrictions, combined with bans on phosphates in detergents, are part of why "normal" cycles tend to take a couple of hours now. Extra time is the most straightforward way to clean better when you can't use much water or energy.

It's also true that some people are unhappy with their dishwasher performance. Wirecutter gets plenty of comments about this problem from readers, and the Competitive Enterprise Institute received a trove of similar complaints for the petition it put forth to the DOE.

The two trends have some relationship, but they aren't the same problem. Crappy cleaning performance and long cycles aren't an inevitable outcome of efficiency standards. If your dishwasher is slow and sucks (and a better detergent doesn't fix the problem), blame the company that built it. Several brands already make fast, high-performing dishwashers that are efficient and reasonably priced. What's everybody else's excuse? A better writer would have something pithy to say here about markets working properly.

What's next for dishwasher efficiency?

Trump's new fast-dishwasher rule could get erased before the DOE even gets a chance to set any guidelines: President Joe Biden put the rule under review on his first day in office as one target (among many other Trump-era efficiency re-regulations and sidesteps) of a massive executive order.

Before Biden even took office, several advocacy groups and states had already sued the federal government over the new rule. Joe Vukovich, an efficiency advocate at the Natural Resources Defense Council (one of the plaintiffs), described it as "an illegal end-run" around existing anti-backsliding laws that are meant to prevent the loosening of efficiency standards. The Competitive Enterprise Institute and other pro-industry groups have signaled that they'll fight to uphold the new classification in court.

The manufacturers just want the status quo: Through their trade group, they actually came out against (PDF) Trump's new fast-dishwasher rule, citing research that most owners are already happy with their dishwashers' quick cycles. The group also came out in favor (PDF) of "sunsetting" the Energy Star program for dishwashers—essentially locking the current, very efficient guidelines in place for the foreseeable future. That would free them from (what they claim is) the grind of designing for and complying with new guidelines two or three times per decade. They also claim that "products are nearing maximum energy and water efficiency under available technology" and that further tightening the guidelines would result in only "limited energy savings and very long payback periods" compared with a dishwasher that doesn't meet Energy Star standards.

Dishwashers are indeed already impressively efficient. The Obama-era DOE even declined in 2016 to tighten the dishwasher standards over the 2013 levels. The savings are especially dramatic compared with hand washing. It seems counterintuitive that an entire dishwasher cycle is more efficient than 15 minutes of manual scrubbing and rinsing, but that's how it is. The thirstiest dishwasher we know of uses about 8 gallons of water on its heavy cycle, which is about what you'd use in four or five minutes with the faucet running. The EPA

estimates an average savings of $400 in utility costs compared with hand washing over the dishwasher's lifetime, split pretty evenly between water and energy. Even if the real figure is half that much, that's pretty good for something that saves you so much time and effort, too.

If dishwashers can already be quick and efficient and not-so-tightly regulated, would anything even change if the Trump rule were to be finalized? If the goal is a one-hour wash that could consistently blast away baked-on foods even with a mediocre detergent, it sounds like the dishwashers would probably be reengineered.

Sood, the former Bosch manager, guessed that the manufacturers could push the existing designs to work harder in short cycles, but the parts might wear out too fast. Alona Wells, a current senior manager at Bosch (one of the companies that already have a great one-hour cycle), said that in theory, yes, Bosch would probably redesign the machines somewhat. Jason Mathew, a senior director at Whirlpool, said that brand would have to "tailor the design, the parts, the system, kind of the performance algorithms and tune all those to deliver that target result."

Sam Kazman, general counsel for the Competitive Enterprise Institute and the driving force behind the DOE petition, put it this way: "Ultimately, if there's really no need for faster models, then they won't sell and our opponents needn't worry. Our petition would in no way restrict the sale of today's high-efficiency machines; it would just give people an option. And judging from the comments, a lot of people want that option."

They already have it.

EPA approves new selenium standards for Lake Koocanusa
https://dailyinterlake.com/news/2021/mar/02/epa-approves-new-selenium-standards-lake-koocanusa/
By WILL LANGHORNE
The Western News | March 2, 2021 9:31 AM

The U.S. Environmental Protection Agency has given its stamp of approval to new selenium standards for Lake Koocanusa and the Kootenai River.

Laura Jenkins, media officer for EPA Region 8, said in a press statement that the federal agency backed the levels proposed by the Montana Department of Environmental Quality on Feb. 25. Under the Clean Water Act, the EPA is responsible for evaluating water quality standards proposed by state environmental agencies.

In December, DEQ's Board of Environmental Review voted in favor of reining in selenium levels for the lake and reservoir. Although significantly more restrictive than those applicable to most state waters, the levels correspond with federally advised standards and methods of approving standards for specific sites.

In a statement, EPA officials said Montana's standards for the Kootenai River now match those in place for the river in Idaho.

More than six years of research conducted by federal, state, tribal and Canadian scientists determined that levels of selenium in Lake Koocanusa and the Kootenai River were putting local aquatic ecosystems at risk. While selenium is necessary in small concentrations for animals and some plants, it can compromise the reproductive systems of certain fish species at elevated levels.

The overwhelming majority of selenium found in local waterways comes from upstream Canadian mines operated by Teck Resources. While the levels approved by the state and federal agencies will not regulate the amount of selenium dumped into waters north of the border, officials said the standards would help the federal government in its negotiations with Canada over the issue.

Local elected officials have raised concerns that the new standards are unnecessarily restrictive and could hamper development in Lincoln County. While State Sen. Mike Cuffe, R-Eureka, said he is in favor of protecting local waters, he opposed DEQ's decision in December, saying the standards could create another hurdle for timber, mining and real estate projects.

Darcy O'Connor, water division director for EPA Region 8, said in December the levels could only be used to moderate activities that could add selenium to the lake and river. During a January Libby City Council meeting, Dave Hadden, director of Headwaters Montana, said commercial work in the county would be unlikely to add selenium to the waterways due to the geology of the area.

Lincoln County Commissioner Jerry Bennett worried in December that the strict selenium standards could lead the state to declare Lake Koocanusa an impaired body of water. If this were to happen, Bennett said fishing outfitters might have trouble attracting clients.

Local guides, however, have come out in support of the new standards. Tim Linehan, of Linehan Outfitting Co., said clients had asked him about selenium in the river and reservoir before the new standards were approved. Since guides release their catch, clients aren't concerned about ingesting selenium. A steep decline in the fish populations in the river due to elevated selenium levels, however, would be a deterrent for anglers.

The Libby City Council voted down a resolution of support for the new standards during a Jan. 19 meeting. The following day, Troy City councilors expressed support for continued research.

EPA FINALIZES ALLOCATION FORMULA FOR SEWER OVERFLOW AND STORMWATER REUSE GRANTS PROGRAM

https://www.estormwater.com/combined-sewer-overflow/epa-finalizes-allocation-formula-sewer-overflow-and-stormwater-reuse-grants

BY CRISTINA TUSER

MAR 02, 2021

EPA announced an allocation formula for the Sewer Overflow and Stormwater Reuse Municipal Grants Program.

EPA published a notice in the Federal Register announcing an allocation formula for the Sewer Overflow and Stormwater Reuse Municipal Grants Program.

EPA is required to establish a formula to allocate proportional shares of amounts appropriated to state entities to fund actions that will help manage combined sewer overflows, sanitary sewer overflows, and storm water, the notice said.

The formula considers the infrastructure needs submitted in the latest EPA Clean Watersheds Needs Survey, along with additional information considered by the EPA administrator, reported the EPA. The CWNS includes and documents identified capital investment needs for SSO correction, CSO correction and storm water management.

The new allocation formula distributes funds to states based on a weighted scale, including: the most recent CWNS (50%), total population (16.7%), urban population (16.7%), and annual average precipitation (16.7%), according to the EPA.

The funding for this Program was originally authorized 20 years ago but money was never appropriated until the 2018 and 2019 America's Water Infrastructure Act process, which secured $28 million and $40 million in appropriations, according to National Association of Clean Water Agencies (NACWA).

The proposed precipitation factor for each state is the annual average amount of precipitation collected from the past 10 years of data from the National Oceanographic and Atmospheric Association (NOAA) National Centers for Environmental Information, Climate at a Glance: Statewide Time Series, according to the EPA.

For each state, the minimum state allocation and the need allocation are combined to equal the final state allocation. EPA did not change the allocation formula from its proposed version to its final version.

NACWA stated that the bulk of the allocation formula relies on the CWNS, which often has a significant time lag with its data, according to NACWA.

EPA settles case with Washington seafood processor over discharge violations
https://www.watertechonline.com/industry/food-beverage/article/14198544/epa-settles-case-with-washington-seafood-processor-over-discharge-violations
Mar 2nd, 2021

The U.S. Environmental Protection Agency recently settled with South Bend Products over federal Clean Water Act violations at the company's South Bend, Washington, seafood processing facility.

South Bend Products, a seafood preparation and processing facility, specializes in salmon and crab processing, and also periodically processes razor clams, black cod, rockfish and halibut.

EPA inspected the South Bend facility in 2017. After reviewing facility records, EPA identified violations of the South Bend facility's wastewater discharge permit, including:

- Exceeded discharge limits
- Insufficient monitoring frequency
- Incorrect sampling, and
- Incomplete or inadequate reporting

As part of the settlement, the company agreed to pay a penalty of $101,630. In addition to paying the penalty, the company has implemented new processes and technologies to address compliance challenges at its South Bend plant.

By improving its effluent treatment South Bend Products has taken steps to reduce the pollutant Total Residual Chlorine in its discharge. The company also established new sampling procedures to adequately monitor for other pollutants such as Total Suspended Solids, Biological Oxygen Demand, and Oil and Grease. Collectively, these measures serve to improve South Bend Products' discharge to the waters of Willapa River and Bay.

This settlement furthers EPA's national compliance initiative to reduce significant noncompliance and improve surface water quality by assuring dischargers comply with National Pollutant Discharge Elimination System (NPDES) permit requirements. For more information on this initiative, please visit: https://www.epa.gov/enforcement/national-compliance-initiative-reducing-significant-non-compliance-national-pollutant.

Appointment

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 9/23/2016 3:39:29 PM
To: Davis, Kable [Davis.Kable@epa.gov]; Goodis, Michael [Goodis.Michael@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Knorr, Michele [Knorr.Michele@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]

Subject: Seresto (flumethrin); 6(a)(2) letter discussion
Location: DCRoomPYS7621B/Potomac-Yard-One

Start: 9/26/2016 1:00:00 PM
End: 9/26/2016 1:30:00 PM
Show Time As: Busy

Required Attendees: Goodis, Michael; Guilaran, Yu-Ting; Vogel, Dana; Knorr, Michele; Perlis, Robert; Echeverria, Marietta; Arrington, Linda; Miller, David; Biscoe, Melanie; Piansay, Maria; Breeden-Alemi, Julie

Appointment

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 8/1/2016 5:44:55 PM
To: Adler, Bonnie [Adler.Bonnie@epa.gov]

Subject: Accepted: Flumethrin TEAM meeting on Seresto - HED update - call in info below...
Location: DCRoomPYS9261/Potomac-Yard-One

Start: 8/4/2016 1:00:00 PM
End: 8/4/2016 2:00:00 PM
Show Time As: Busy

Appointment

From: Adler, Bonnie [Adler.Bonnie@epa.gov]
Sent: 8/1/2016 5:41:16 PM
To: Adler, Bonnie [Adler.Bonnie@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Atwood, Donald [Atwood.Donald@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Britton, Wade [Britton.Wade@epa.gov]; Cook, Colwell [cook.colwell@epa.gov]; Craig, Evisabel [Craig.Evisabel@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; English, LisaRenee [English.LisaRenee@epa.gov]; Hanson, Charmaine [Hanson.Charmaine@epa.gov]; Hawkins, Monica [Hawkins.Monica@epa.gov]; Holmes, Jean [Holmes.Jean@epa.gov]; VanAlstine, Julie [VanAlstine.Julie@epa.gov]; White, Katrina [White.Katrina@epa.gov]

Subject: Flumethrin TEAM meeting on Seresto - HED update - call in info below...
Location: DCRoomPYS9261/Potomac-Yard-One

Start: 8/4/2016 1:00:00 PM
End: 8/4/2016 2:00:00 PM
Show Time As: Busy

Required Attendees: Arrington, Linda; Atwood, Donald; Biscoe, Melanie; Britton, Wade; Cook, Colwell; Craig, Evisabel; Davis, Donna; Davis, Kable; Echeverria, Marietta; English, LisaRenee; Hanson, Charmaine; Hawkins, Monica; Holmes, Jean; VanAlstine, Julie; White, Katrina

Message

From: Lowe, Kelly [Lowe.Kelly@epa.gov]
Sent: 10/7/2016 12:07:01 PM
To: Olinger, Christine [Olinger.Christine@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Jennings, Susan [Jennings.Susan@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]
CC: Tyler, Jennifer-R [Tyler.Jennifer-R@epa.gov]; Perron, Monique [Perron.Monique@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Dawson, Jeffrey [Dawson.Jeff@epa.gov]; Reaves, Elissa [Reaves.Elissa@epa.gov]; Britton, Wade [Britton.Wade@epa.gov]
Subject: RE: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations
Attachments: D399719.mem (2013 RA).docx

Hi everyone,

I didn't receive the Region 9 document so I haven't looked at that, but just to follow up on what Chris sent regarding the assessment for imidacloprid and pet collars. The pet collar use was most recently assessed in 2013 – that risk assessment is attached, and has an updated assessment from the one Chris linked to, that used the 2012 Residential SOPs to assess the pet collar use. No risks were identified. However, it should be noted that these uses will be reevaluated soon for the DRA for imidacloprid (due the end of this year), and there have been some new concerns recently about the actual formulation of pet collars. It is not clear Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Kelly Lowe
Health Effects Division
Office of Pesticide Programs
703.347.8989

From: Olinger, Christine
Sent: Thursday, October 06, 2016 5:26 PM
To: Davis, Kable <Davis.Kable@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>; Arrington, Linda <Arrington.Linda@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Jennings, Susan <Jennings.Susan@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>
Cc: Tyler, Jennifer-R <Tyler.Jennifer-R@epa.gov>; Perron, Monique <Perron.Monique@epa.gov>; Vogel, Dana <Vogel.Dana@epa.gov>; Dawson, Jeffrey <Dawson.Jeff@epa.gov>; Reaves, Elissa <Reaves.Elissa@epa.gov>; Lowe, Kelly <Lowe.Kelly@epa.gov>
Subject: RE: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

Bo –
HED assessed the imidacloprid pet collar use in 2012 – below is a link to the evaluation. I'm confused by the Region 9 statement as well. Maybe they haven't seen the imidacloprid assessment? Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

I am compressed on Friday, but I have copied a few people who are working tomorrow (as well as HED division management) and may be helpful if you have any further questions that can't wait until Tuesday.

Chris O.

Link to ORE review - imid pet collar

~~~~~~

Christine Olinger, Acting Chief
Risk Assessment Branch I
US Environmental Protection Agency
Office of Pesticide Programs/Health Effects Division
1200 Pennsylvania Ave. NW (7509P)
Washington DC 20460
Deliveries: 2777 Crystal Drive (Room 10751); Arlington, VA 22202
Phone: 703-305-5406
Fax: 703-305-5147

Visit: epa.gov/pesticides

From: Davis, Kable
Sent: Thursday, October 06, 2016 5:03 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>; Olinger, Christine <Olinger.Christine@epa.gov>; Arrington, Linda <Arrington.Linda@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Jennings, Susan <Jennings.Susan@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>
Subject: FW: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

Everyone –

Please see the email below and the attached document from Region 9. CDC has initiated a program to put Seresto collars on dogs after an outbreak of Rocky Mountain Spotted Fever (RMSF) within some American Indian communities in Arizona. Region 9 would like to distribute this sheet that provides some general information about both RMSF and the Seresto collar itself. They would like any comments from us by next Wednesday (10/12). My initial comments are below:

Ex. 5 Deliberative Process (DP)

I would be happy to schedule a meeting if people think this warrants a discussion. Otherwise, please provide any comments you have by COB Tuesday.

Thanks much,
Bo

From: Saunders, Jennifer
Sent: Thursday, October 06, 2016 12:02 PM
~~~~~~

To: Davis, Kable <Davis.Kable@epa.gov>
Subject: FW: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

---

From: Overbey, Dian
Sent: Thursday, October 06, 2016 11:58 AM
To: Jennings, Susan <Jennings.Susan@epa.gov>; Saunders, Jennifer <Saunders.Jennifer@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>
Subject: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

Attached is an information sheet developed by Region 9 that deals with RMSF and the use of Seresto flea and tick collars. CDC had initiated a program to put Seresto collars on dogs after an outbreak of the tick-bourne disease in Indian Country in Arizona. Region 9 is thinking of distributing this as a Region 9 information sheet that can either stand alone or be attached to tribal newsletters. Patti TenBrook has asked for feedback from headquarters. We'd appreciate your comments by next Wednesday, October 12.

Thanks,

Dian D. Overbey
Communication Services Branch
Field and External Affairs Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Potomac Yard S-8927
(703) 305-5018

Message

From: Arrington, Linda [Arrington.Linda@epa.gov]
Sent: 10/6/2016 10:12:48 PM
To: Olinger, Christine [Olinger.Christine@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Jennings, Susan [Jennings.Susan@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]
CC: Tyler, Jennifer-R [Tyler.Jennifer-R@epa.gov]; Perron, Monique [Perron.Monique@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Dawson, Jeffrey [Dawson.Jeff@epa.gov]; Reaves, Elissa [Reaves.Elissa@epa.gov]; Lowe, Kelly [Lowe.Kelly@epa.gov]
Subject: RE: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

Bo

I have some additional concerns with the Seresto Collar section

Ex. 5 Deliberative Process (DP)

Linda Arrington, Branch Chief
RMIB 5
Pesticide Re-evaluation Division
Office 703 305 6249
Fax 703 308 8005

From: Olinger, Christine
Sent: Thursday, October 06, 2016 5:26 PM
To: Davis, Kable <Davis.Kable@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>; Arrington, Linda <Arrington.Linda@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Jennings, Susan <Jennings.Susan@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>
Cc: Tyler, Jennifer-R <Tyler.Jennifer-R@epa.gov>; Perron, Monique <Perron.Monique@epa.gov>; Vogel, Dana <Vogel.Dana@epa.gov>; Dawson, Jeffrey <Dawson.Jeff@epa.gov>; Reaves, Elissa <Reaves.Elissa@epa.gov>; Lowe, Kelly <Lowe.Kelly@epa.gov>
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Chris O.

Link to ORE review - imid pet collar

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Christine Olinger, Acting Chief
Risk Assessment Branch I
US Environmental Protection Agency
Office of Pesticide Programs/Health Effects Division
1200 Pennsylvania Ave. NW (7509P)
Washington DC 20460
Deliveries: 2777 Crystal Drive (Room 10751); Arlington, VA 22202
Phone: 703-305-5406
Fax: 703-305-5147

Visit: epa.gov/pesticides

From: Davis, Kable
Sent: Thursday, October 06, 2016 5:03 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>; Olinger, Christine <Olinger.Christine@epa.gov>; Arrington, Linda <Arrington.Linda@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Jennings, Susan <Jennings.Susan@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>
Subject: FW: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

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From: Saunders, Jennifer
Sent: Thursday, October 06, 2016 12:02 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Subject: FW: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

---

From: Overbey, Dian
Sent: Thursday, October 06, 2016 11:58 AM
To: Jennings, Susan <Jennings.Susan@epa.gov>; Saunders, Jennifer <Saunders.Jennifer@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>
Subject: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

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Thanks,

Dian D. Overbey
Communication Services Branch
Field and External Affairs Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Potomac Yard S-8927
(703) 305-5018

Message

From: Jennings, Susan [Jennings.Susan@epa.gov]
Sent: 10/6/2016 11:26:49 PM
To: Davis, Kable [Davis.Kable@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Olinger, Christine [Olinger.Christine@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]
Subject: Re: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

Additional info:

CDC has distributed these collars intermittently since the first day they were registered. We rushed this registration so that CDC could use them in their study.

CDC uses these collars because they last longer than any other on the market. These are community dogs, so many of them don't really have an owner who will change out the collars. The seresto collars last the entire tick season.

Sent from my iPhone

> On Oct 6, 2016, at 5:03 PM, Davis, Kable <Davis.Kable@epa.gov> wrote:
>
> Everyone –
>
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> To: Davis, Kable <Davis.Kable@epa.gov>
> Subject: FW: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations
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> From: Overbey, Dian
> Sent: Thursday, October 06, 2016 11:58 AM
> To: Jennings, Susan <Jennings.Susan@epa.gov<mailto:Jennings.Susan@epa.gov>>; Saunders, Jennifer <Saunders.Jennifer@epa.gov<mailto:Saunders.Jennifer@epa.gov>>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov<mailto:Breeden-Alemi.Julie@epa.gov>>
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> Communication Services Branch
> Field and External Affairs Division
> Office of Pesticide Programs
> U.S. Environmental Protection Agency
> Potomac Yard S-8927
> (703) 305-5018
>
> <DRAFT_Seresto flea collars_100416 ddo edits.docx>

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 10/6/2016 9:03:20 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Olinger, Christine [Olinger.Christine@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Jennings, Susan [Jennings.Susan@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]
Subject: FW: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations
Attachments: DRAFT_Seresto flea collars_100416 ddo edits.docx

Everyone –

Please see the email below and the attached document from Region 9. CDC has initiated a program to put Seresto collars on dogs after an outbreak of Rocky Mountain Spotted Fever (RMSF) within some American Indian communities in Arizona. Region 9 would like to distribute this sheet that provides some general information about both RMSF and the Seresto collar itself. They would like any comments from us by next Wednesday (10/12). My initial comments are below:

Ex. 5 Deliberative Process (DP)

I would be happy to schedule a meeting if people think this warrants a discussion. Otherwise, please provide any comments you have by COB Tuesday.

Thanks much,
Bo

From: Saunders, Jennifer
Sent: Thursday, October 06, 2016 12:02 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Subject: FW: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

From: Overbey, Dian
Sent: Thursday, October 06, 2016 11:58 AM
To: Jennings, Susan <Jennings.Susan@epa.gov>; Saunders, Jennifer <Saunders.Jennifer@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>
Subject: Region 9 information sheet on Seresto Flea and Tick collars used to reduce occurrence of Rocky Mountain spotted fever on Indian reservations

Attached is an information sheet developed by Region 9 that deals with RMSF and the use of Seresto flea and tick collars. CDC had initiated a program to put Seresto collars on dogs after an outbreak of the tick-bourne disease in Indian

Country in Arizona. Region 9 is thinking of distributing this as a Region 9 information sheet that can either stand alone or be attached to tribal newsletters. Patti TenBrook has asked for feedback from headquarters. We'd appreciate your comments by next Wednesday, October 12.

Thanks,

Dian D. Overbey
Communication Services Branch
Field and External Affairs Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Potomac Yard S-8927
(703) 305-5018

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 11/14/2016 4:51:18 PM
To: Miller, David [Miller.DavidJ@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]
Subject: RE: Noteworthy NPIC Incident - Soresto flea collar

Agreed. I'm actually going to mention all of the "side commentary" during this Wednesday's Incident Screening Team meeting.

From: Miller, David
Sent: Monday, November 14, 2016 11:48 AM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>
Subject: RE: Noteworthy NPIC Incident - Soresto flea collar

Nice answer, Bo.

Ex. 5 Deliberative Process (DP)

David.

From: Davis, Kable
Sent: Monday, November 14, 2016 8:27 AM
To: Miller, Robert <Miller.Robert@epa.gov>; Rivera-Lupianez, Ana <Rivera-Lupianez.Ana@epa.gov>; Chen, Jonathan <Chen.Jonathan@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>; Panger, Melissa <Panger.Melissa@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>; Sell, Nathan <Sell.Nathan@epa.gov>; Tanner, Lee <Tanner.Lee@epa.gov>
Cc: Dumas, Richard <Dumas.Richard@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>; Hopkins, Yvette <Hopkins.Yvette@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Mastrota, Nicholas <Mastrota.Nicholas@epa.gov>
Subject: RE: Noteworthy NPIC Incident - Soresto flea collar

Bob –

Reported adverse effects to domestic animals is being reviewed during Registration Review for flumethrin. The PWP included the following language:

"During the registration review of flumethrin, the Agency anticipates the need to conduct a post-market pharmacovigilance review of the reported adverse events to domestic animals. These analyses may include: a

summary of number of incidents (Level 1), reporting odds ratio (Level 2), incident rate ratio (Level 3), incident rate ratio by product, active ingredient or symptom (Level 4), and/or clinical review of case reports."

I hope this helps.
Bo

From: Miller, Robert
Sent: Monday, November 14, 2016 8:19 AM
To: Rivera-Lupianez, Ana <Rivera-Lupianez.Ana@epa.gov>; Chen, Jonathan <Chen.Jonathan@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Panger, Melissa <Panger.Melissa@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>; Sell, Nathan <Sell.Nathan@epa.gov>; Tanner, Lee <Tanner.Lee@epa.gov>
Cc: Dumas, Richard <Dumas.Richard@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>; Hopkins, Yvette <Hopkins.Yvette@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Mastrota, Nicholas <Mastrota.Nicholas@epa.gov>
Subject: RE: Noteworthy NPIC Incident - Soresto flea collar

Hi Ana,

Thank you for the Seresto dog collar incident report. **Ex. 5 Deliberative Process (DP)**?

Bob

Robert A. Miller
6(a)(2) Coordinator
Information Technology and Resource Management Division
EPA Office of Pesticide Programs
United States Environmental Protection Agency
1200 Pennsylvania Avenue, N.W., Washington D.C.

(703) 347-8012
miller.robert@epa.gov

From: Rivera-Lupianez, Ana
Sent: Monday, November 14, 2016 7:55 AM
To: Chen, Jonathan <Chen.Jonathan@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Miller, Robert <Miller.Robert@epa.gov>; Panger, Melissa <Panger.Melissa@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>; Sell, Nathan <Sell.Nathan@epa.gov>; Tanner, Lee <Tanner.Lee@epa.gov>
Cc: Dumas, Richard <Dumas.Richard@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>; Hopkins, Yvette <Hopkins.Yvette@epa.gov>
Subject: Fw: Noteworthy NPIC Incident - Soresto flea collar

Good morning,

FYI
Seresto flea collar incident; ais - imidacloprid, flumethrin.

Thanks,
Ana

Ana Rivera-Lupiáñez
Office of Pesticide Programs
Environmental Protection Agency
rivera-lupianez.ana@epa.gov
(703) 308-6841

From: Hallman, Amy S <Amy.Hallman@oregonstate.edu>
Sent: Friday, November 11, 2016 11:12 AM
To: Rivera-Lupianez, Ana
Cc: Kaci.Buhl@oregonstate.edu; Jenkins, Jeffrey James
Subject: Noteworthy NPIC Incident - Soresto flea collar

Hello Ana,

We had an incident related to Soresto flea collars reported recently.

Case 10548: An owner reported a seizure for one dog and shaking for another, among other symptoms, after Soresto flea collars (active ingredients imidacloprid, flumethrin) were applied to her five dogs. The owner has reported removing the collars from all her dogs.

Kind regards,
Amy

--
Amy S. Hallman, MS
Interim Project Coordinator
National Pesticide Information Center
Oregon State University
Department of Environmental and Molecular Toxicology
amy.hallman@oregonstate.edu
541-737-6093

Message

From: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Sent: 9/28/2016 2:28:20 PM
To: Housenger, Jack [Housenger.Jack@epa.gov]
CC: Goodis, Michael [Goodis.Michael@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Keigwin, Richard [Keigwin.Richard@epa.gov]
Subject: FYI: Draft flumethrin PWP with YTG comments
Attachments: image2016-09-27-210133.pdf

Jack
FYI, here is where the document is for Seresto. I commented on Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP) Please let us know if you have any thoughts on this. Thanks.

Regards,

Yu-Ting Guilaran, P.E.
Director

Pesticide Re-evaluation Division (PRD)
Office of Pesticide Programs
Office of Chemical Safety and Pollution Prevention
(tel) 703 308 0052
(fax)703 308 8005
Mail code 7508P
Room number PY S9623

From: Bloom, Jill
Sent: Wednesday, September 28, 2016 8:59 AM
To: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Cc: Biscoe, Melanie <Biscoe.Melanie@epa.gov>
Subject: FW: scan of flumethrin PWP with YTG comments

Attached.

Jill

From: VA-PYS-9251-M@EPA.GOV [mailto:VA-PYS-9251-M@EPA.GOV]
Sent: Tuesday, September 27, 2016 9:02 PM
To: Bloom, Jill <Bloom.Jill@epa.gov>
Subject:

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 9/23/2016 4:49:12 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: Seresto Language

Below is my initial draft. Let me know what you think.

Ex. 5 Deliberative Process (DP)

Appointment

From: Jewell, Shannon [jewell.shannon@epa.gov]
Sent: 9/20/2016 12:46:39 PM
To: Goodis, Michael [Goodis.Michael@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Knorr, Michele [knorr.michele@epa.gov]; Keigwin, Richard [Keigwin.Richard@epa.gov]
CC: Perlis, Robert [Perlis.Robert@epa.gov]

Subject: Seresto Pet Collar Briefing
Attachments: Seresto Briefing Document.docx
Location: 12100 PY

Start: 9/20/2016 3:00:00 PM
End: 9/20/2016 4:00:00 PM
Show Time As: Tentative

Required Attendees: Goodis, Michael; Echeverria, Marietta; Davis, Kable; Rosenblatt, Daniel; Guilaran, Yu-Ting; Arrington, Linda; Biscoe, Melanie; Piansay, Maria; Vogel, Dana; Miller, David; Rossmeisl, Colleen; Knorr, Michele; Keigwin, Richard
Optional Attendees: Perlis, Robert

9/20/16 Update:

Good morning,

Please see the one-pager attached, and note that the meeting will be held in room 12100.

Seresto Briefing Document.docx

Briefing with Jack regarding an upcoming meeting with Bayer about the Seresto pet collar preceding the meeting with Bayer to take place on Thursday, September 22nd. A one-pager will be forthcoming and added to this invitation.

Meeting requested by Kable Bo Davis on 9/13/16
Scheduled by Shannon Jewell

EPA-internal, confidential, deliberative

Seresto Briefing Document

Product Description

- Seresto is a dog and cat collar, which is intended to control fleas and ticks for up to 8 months.
- The collar contains 4.5% flumethrin and 10.0% imidacloprid. This is the only use for flumethrin.

Timeline

- **July 27, 2015:** EPA received a press inquiry alerting us to an alleged high number of reported pet incidents.
- **August 5, 2015:** Bayer submitted sales information for Seresto.
- **August 28, 2015:** Bayer submitted incident data using template suggested by EPA.
- **December 16, 2015:** RD and HED briefed upper management on the status of review for the incident data.
- **July 18, 2016:** OPP received the incident report outlining the overall findings and conclusions of PMRA's Seresto collar review.
- **August 10, 2016:** OPP was informed, via conference call, that PMRA would not register Seresto in Canada. As a result, Bayer withdrew the submission and requested PMRA not share any further documents with EPA.
- **September 1, 2016:** OPP completes its draft review of the incident data and PMRA's causality analysis. The document has not been finalized.
- **September 2, 2016:** EPA receives Bayer's critique of PMRA's Animal Incident Assessment. The document is in the process of being reviewed.
- **September 22, 2016:** Bayer has requested a meeting with EPA to discuss the scope of the flumethrin report that is to be made public by the end of September for Registration Review.

Agency Review of Incidents & Causality Analysis

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP) - Ex. 4 Potential CBI

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Note – OGC is attending to address any legal concerns.

Appointment

From: Piansay, Maria [Piansay.Maria@epa.gov]
Sent: 9/19/2016 11:46:22 AM
To: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]
CC: Knorr, Michele [knorr.michele@epa.gov]; Goodis, Michael [Goodis.Michael@epa.gov]

Subject: Flumethrin Bayer Meeting
Location: DCRoomPYS9261/Potomac-Yard-One

Start: 9/22/2016 6:00:00 PM
End: 9/22/2016 7:00:00 PM
Show Time As: Tentative

Required Attendees: Guilaran, Yu-Ting; Vogel, Dana; Rosenblatt, Daniel; Echeverria, Marietta; Miller, David; Rossmeisl, Colleen; Arrington, Linda; Davis, Kable; Biscoe, Melanie
Optional Attendees: Knorr, Michele; Goodis, Michael

Meeting Agenda from Bayer

1. To discuss status and timing of the documents EPA intends to release in September regarding Flumethrin and the Flumethrin-containing products;
2. To review timing of registration review for the Flumethrin-containing products and inclusion in the pyrethroid registration review;
3. To understand references and approach in these documents to Seresto;
4. To express Bayer's perspective on potential references to Flumethrin and Seresto;
5. To understand the anticipated scope of the registration review, and the expected schedule for the conduct of the review;
6. For Bayer to understand from the Agency its intentions and next steps in this process.

Attending from Bayer will be:

- Joyce Lee, President, Commercial Operations North America, Bayer Animal Health
- Robert Zolynas, Vice President Research and Development, North America, Bayer Animal Health
- Jessica Monachello, Assistant General Counsel Bayer Animal Health
- Roger R. Martella Jr., Outside Counsel, Sidley Austin LLP

Message

From: Arrington, Linda [Arrington.Linda@epa.gov]
Sent: 9/15/2016 10:44:53 PM
To: Holmes, Jean [Holmes.Jean@epa.gov]; White, Katrina [White.Katrina@epa.gov]; Encarnacion, Ideliz [Encarnacion.Ideliz@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; VanAlstine, Julie [VanAlstine.Julie@epa.gov]; Hawkins, Monica [Hawkins.Monica@epa.gov]; Craig, Evisabel [Craig.Evisabel@epa.gov]; Britton, Wade [Britton.Wade@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]; Cook, Colwell [cook.colwell@epa.gov]; Atwood, Donald [Atwood.Donald@epa.gov]; English, LisaRenee [English.LisaRenee@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]
CC: Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]
Subject: FW: flumethrin documents
Attachments: Team members.081816.doc; 036007_433710_PF and PRA_07-05-16.pdf; Flumethrin (036007) Label Data Report.xlsx; Flumethrin (036007) HED Master Label Report.xlsx; Flumethrin (036007) General Chemical (Issues) Report.xlsx; D434133 Scoping Doc.mem.pdf; D435503 Incident.090716.mem.pdf; HED Risk assessment for Pet CollarsEPA-HQ-OPP-2011-0013-0004.pdf; Seresto - Human Exposure Analysis document ; Draft Flumethrin PWP mp 090916 lga comments.docx

Good evening everyone,

I am sending this PWP for Flumethrin on behalf of Maria Piansay. As we are nearing the end of the quarter time is of the essence. I am requesting a very quick turnaround time so that I can get this signed before the end of the month. I am asking for comments back to Maria by 12:00 Tuesday 9/20. This is one of the shorter PWPs so hopefully you can meet my deadline. Please contact me if you have any questions.

Thanks again for helping my branch meet its deliverables.

Linda Arrington, Branch Chief
RMIB 5
Pesticide Re-evaluation Division
Office 703 305 6249
Fax 703 308 8005

Team Members for Flumethrin

EFED (ERB 4): Jean Holmes (BC), Katrina White (on leave), Ideliz Encarnacion (acting RAPL)

HED (RAB 6): Donna Davis (BC), Julie VanAlstine, Monica Hawkins, Evisabel Craig, Wade Britton, Shanna Recore

BEAD: Colwell Cook (TL), Don Atwood (SIAB), LisaRenee English (BAB)

RD (IVB1): Marietta Echeverria (BC), Kable Davis (PM3), Laura Bacon (acting PM4)

PRD: Linda Arrington (BC), Melanie Biscoe (TL), Maria Piansay (CRM)

Registrant contact: Dr. Bruce Martin
Bayer Healthcare LLC
Animal Health Division
PO Box 390
Shawnee Mission, KS 66201-0390
Phone: (913)268-2779

Or

Doug Spilker
Work: (913)268-2751
Cell: (816)506-3102

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

PC Code: 036007
DP Code: 433710
July 5, 2016

MEMORANDUM

SUBJECT: Flumethrin. Preliminary Problem Formulation and Ecological Risk Assessment and Effects Determination in Support of Registration Review.

TO: Bonnie Adler, Chemical Review Manager
Melanie Biscoe, Team Leader
Linda Arrington, Branch Chief
Risk Management and Implementation Branch V
Pesticide Re-evaluation Division (7508P)

Ideliz Negron Encarnacion
2016.07.06 17:58:20 -04'00'

FROM: Ideliz Negrón-Encarnación, Ph.D., Risk Assessment Process Leader (Acting)
Environmental Risk Branch IV
Environmental Fate and Effects Division (7507P)

REVIEWED BY: Thomas Steeger, Ph.D., Senior Science Advisor
Environmental Risk Branch IV
Environmental Fate and Effects Division (7507P)

THOMAS STEEGER
Digitally signed by THOMAS STEEGER
DN: c=US, o=U.S. Government, ou=USEPA, ou=Staff, cn=THOMAS STEEGER, dnQualifier=0000021782
Date: 2016.07.07 09:01:58 -04'00'

THROUGH: Jean Holmes, D.V.M., Branch Chief
Environmental Risk Branch IV
Environmental Fate and Effects Division (7507P)

JEAN HOLMES
Digitally signed by JEAN HOLMES
DN: c=US, o=U.S. Government, ou=USEPA, ou=Staff, cn=JEAN HOLMES, dnQualifier=0000005813
Date: 2016.07.07 09:30:43 -04'00'

The Environmental Fate and Effects Division (EFED) has completed the combined problem formulation and preliminary ecological risk assessment and federally listed, threatened, and endangered species (also referred to as "listed" species) effects determination in support of the Registration Review of the insecticide flumethrin (PC Code 036007). Flumethrin is used in pet collars for the prevention and treatment of ticks, fleas, and lice on dogs and cats; the pet collars are left up to 8 months on the treated animal. Given the exclusive use of flumethrin in pet collars and that these collars are typically applied to domesticated animals that spend a large proportion of their time indoors, the use of flumethrin is considered to be primarily a use with *de minimus* exposure for non-target organisms. As this use is limited to pets, the product is impregnated in a collar and the active ingredient has low volatility, the likelihood of adverse effects on non-target organism from exposure is considered low. Based on the low likelihood of exposure, the likelihood of adverse effects to listed species is also expected to be low and supports a no effects (NE) determination.

ASSESSMENT

Flumethrin (*RS*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-(*EZ*)-3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate; (CAS No. 69770-45-2) is a synthetic pyrethroid insecticide. Flumethrin is registered as a technical grade active ingredient (TGAI) and in one end-use product (EP)

product (**Table 1**) for use as a pet collar (PNR1427 Insecticide, EPA Reg. No. 11556-155, April 3, 2014) which also includes the neonicotinoid insecticide imidacloprid (CAS 138261-41-3; PC Code 129099). Label directions instruct users to open the container only when the product needs to be used; to fasten the collar around the dog/cat neck; and, to leave the collar in place for up to 8 months.

Table 1. Registered Products for Flumethrin[1,2]

Registration Number	Product Name	% Flumethrin	TGAI/EP[1]
11556-155	PNR1427 Insecticide[3]	4.5	EP
11556-154	Flumethrin Technical	99.2	TGAI

[1] TGAI – technical grade active ingredient. EP – end-use product.
[2] Max 66% *trans* Z-1 and min 34% *trans* Z-2.
[3] This end use product is co-formulated with 10% of imidacloprid.

Since the compound is contained within a collar which is in turn affixed to a domesticated dog or cat, the labeled use and application method of flumethrin limit direct or indirect exposure to outdoor terrestrial areas given that the majority of animals treated primarily reside indoors. While there is potential for exposure to flumethrin vapors due to sublimation from the pet collar, the exposure is expected to be minimal given the chemical's pet-only uses, low vapor pressure (3.9×10^{-9} mm Hg at 25 °C) [1] and that the volatilized fraction is expected to dissipate rapidly through dilution with large volumes of air. In addition, the pet collar use of flumethrin is unlikely to result in exposure to aquatic resources or groundwater as any solubilized material (water solubility 9.7×10^{-5} mg/L at 20 °C) will be diluted as well. Because of the low potential for non-target species to be exposed, only limited data have been submitted for this chemical.

Based on the 2012 Human Health Risk Assessment, flumethrin is considered moderately toxic to terrestrial mammals on an oral, inhalation and dermal exposure basis (Toxicity Category II) and it is not considered an eye or dermal irritant (Toxicity Category IV).[1] There are currently no toxicity data to assess the potential risk to other terrestrial or aquatic organisms from the registered use of flumethrin; however, risks to non-target organisms are not expected due to the low exposure potential.

Threatened/Endangered Species

Because of the predominantly indoor use of the product and low likelihood of exposure for terrestrial and aquatic organisms, there is no reasonable expectation of effects to listed species from the use of the currently registered flumethrin product. Therefore, EPA concludes that the currently registered use of flumethrin in pet collars is not expected to cause direct or indirect effects to federally listed threatened and endangered species. A *No Effect* (NE) determination is made for all listed species, as well as a *No Habitat Modification* determination for all designated critical habitats for the currently registered use of flumethrin.

ENDOCRINE DISRUPTOR SCREENING PROGRAM

As required by Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Food, Drug and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence,

[1] Flumethrin: Human Health Risk Assessment for the Section 3 Registration Action for Cat and Dog Collars.; C. Smith and Marquea King; D392125; 03/06/2012.

ED_005739A_00099203-00002

including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for flumethrin, EPA reviewed available data; however, since the likelihood of exposure to flumethrin is low, toxicity data for the compound have not been submitted. As required by FFDCA section 408(p) though, flumethrin is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals for their potential as an endocrine disruptor. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[2] and includes some pesticides scheduled for registration review and chemicals found in water. Flumethrin was not included in the lists of chemicals for which test orders were issued. In this proposed risk assessment, EPA is making no human health or environmental safety findings associated with the EDSP screening of flumethrin. Before completing the registration review for flumethrin, the Agency will make an EDSP FFDCA section 408(p) determination. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[3]

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[2] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[3] http://www.epa.gov/endo/

ED_005739A_00099203-00003

Label Data Report

Ingredient: Flumethrin (036007)

Current As Of Date : 02/12/16 NDC - No Dosage Conversion ; NS - Not Specified

This is a full report. One EPA registered and accepted Section 3 registration, containing this active ingredient, as of the date of this report, is included

Site Desc	Use Group Desc	Reg#	LUIS Accepted Date	AI%	Formulation Desc	Product Name	Original (Product / A. I.) Max App Rate	Original (Product / A. I.) Max App Unit	A. I. Max App Rate	A. I. Max App Unit	Max # Apps @ Max Rate / CC	Product Max Dose/Year	A. I. Max App Rate/Year	Product Max Dose/CC	A. I. Max Dose/CC	Max # Apps @ Max Rate / Unit of Time	Minimum Retreatment Interval
CATS (ADULTS/KITTENS)	INDOOR RESIDENTIAL	11556-155	4/3/2014	4.5	IC/T	PNR1427 INSECTICIDE	1	collar / 1 animal	NDC	NDC	NS	NS	NS	NS	NS	NS	240 d
DOGS/CANINES (ADULTS/PUPPIES)	INDOOR RESIDENTIAL	11556-155	4/3/2014	4.5	IC/T	PNR1427 INSECTICIDE	1	collar / 1 animal	NDC	NDC	NS	NS	NS	NS	NS	NS	240 d

in this report with the exception of technical and/or manufacturing use products.

Rentry Interval	Application Method Type	Application Method Equipment	Application Method Timing	Incorporation Depth	Buffer Restriction	Disallowed Geo Areas	Allowable Geo Areas	Soil Factor	Percent Organic Matter	PHI (days)
NS	Animal treatment (collar).	Collar	When needed.							
NS	Animal treatment (collar).	Collar	When needed.							

HED Master Label Report

Ingredient: Flumethrin (036007)

Current As Of Date : 02/12/16 NDC - No Dosage Conversion ; NS - Not Specified

This is a full report. One EPA registered and accepted Section 3 registration, containing this active ingredient, as of the date of this report, is inclu

Registration Number	Accepted Date	AI%	Form Desc	Product Name	Residential Use	Use Group	Use Site	Application Method Type	Application Method Equipment	Application Method Timing	Original (Product / A. I.) Max App Rate	Original (Product / A. I.) Max App Unit	A. I. Max App Rate	A. I. Max App Unit	Re - entry Interval
11556-155	4/3/2014	4.5	IC/T	PNR1427 INSECTICIDE	Y	INDOOR RESIDENTIAL	CATS (ADULTS/KITTENS)	Animal treatment (collar).	Collar	When needed.	1	collar / 1 animal	NDC	NDC	NS
11556-155	4/3/2014	4.5	IC/T	PNR1427 INSECTICIDE	Y	INDOOR RESIDENTIAL	DOGS/CANINES (ADULTS/PUPPIES)	Animal treatment (collar).	Collar	When needed.	1	collar / 1 animal	NDC	NDC	NS

ded in this rep

PHI / PGI / PSI
PHI: PGI: PSI:
PHI: PGI: PSI:

General Chemical (Issues) Report

Ingredient: Flumethrin (036007)

Current As Of Date : 02/12/16

This is a full report. One EPA registered and accepted Section 3 registration, containing this active ingredient, as of the date of this report, is included in this report with

Reg. No.	Issue Cat.	Description	Custom Desc	Site	Use group	Application Type	Application Timing	Application Equipment	
11556-155	Restrictions	Custom	For use on dogs and puppies 7 weeks of age and older and up to 18 lbs (8 kg) body weight.	DOGS/CANINES (ADULTS/PUPPIES)	INDOOR RESIDENTIAL	ALL	ALL	ALL	

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: 07-SEP-2016

SUBJECT: **Flumethrin.** Human Health Assessment Scoping Document in Support of Registration Review.

PC Code: 036007
Decision No.: 518360
Petition No.: NA

Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D434133
Registration No.: NA
Regulatory Action: Registration Review Scoping Document
Case No.: None
CAS No.: 69770-45-2
40 CFR: NA

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THROUGH: Donna S. Davis, Branch Chief
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Attached is HED's human health risk assessment scoping document for flumethrin to support Registration Review.

ED_005739A_00099207-00001

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ED_005739A_00099207-00002

Executive Summary

HED has prepared a scoping document to support Registration Review of flumethrin, cyano(4-fluoro-3-phenoxyphenyl)methyl 3-[2-chloro-2-(4-chlorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate, a synthetic pyrethroid insecticide. Flumethrin is registered for use in cat and dog collars that also contain imidacloprid to control ticks, lice, and mites. This scoping document addresses only the active ingredient flumethrin. There are no other registered or pending uses of flumethrin; therefore, food and drinking water assessments are not required. The most recent human health risk assessment was completed in 2012 (Memo, C. Smith, *et al.*, 6-MAR-2012; D392125).

HED has evaluated the status of the human health assessments for flumethrin to determine whether sufficient data are available, and whether any updates are needed to support Registration Review. HED has considered all available data and human health risk assessments for flumethrin with respect to its toxicity, exposure, and usage databases, and the most updated agency science policy and risk assessment methodologies to determine the scope of work necessary to support Registration Review.

Based on the 2007 revised 40 CFR Toxicology Data Requirements, the toxicity database for flumethrin is sufficient to assess risk for non-food uses. As part of Registration Review, the endpoints, doses, and uncertainty/safety factors most recently selected may be re-evaluated according to the most up-to-date HED policy.

There are no registered uses of flumethrin that would result in dietary (food and drinking water) exposures; therefore, residue chemistry data are not needed and dietary exposure (food and drinking water) and quantitative aggregate risk assessments are not required.

The residential exposure database is not adequate to support the Registration Review process for flumethrin. As part of Registration Review, the agency will be reassessing the exposures from the use of pet collars. Previous assessments have considered exposures to flumethrin from the pet collars to be in the liquid form; however, recently, the agency has questioned whether exposure from pet collars is a liquid form, solid form, or some combination of both, which dictates how exposures are calculated. As a result, the agency is seeking information from the registrant on the relative amounts of solids (e.g., dust) or liquids available for exposure as a result of the use of flumethrin-impregnated pet collars. The agency is requesting additional information to inform the risk assessment for post-application residential exposure and plans to work with the registrant to determine the exposure data that can answer this question. A traditional pet transferable residue study (*i.e.*, a petting study) or other study that would inform the Agency's risk assessment may be required. Therefore, an updated residential post-application exposure assessment will be required during Registration Review based upon HED's Residential SOPs, any potential updates to the toxicological PODs, and/or the additional required data received by the Agency that affects exposure estimates.

The last residential assessment was conducted in 2012 (Memo, C. Smith, *et al.*, 6-MAR-2012; D392125). In the 2012 risk assessment, the residential handler exposure and risk estimates indicate that the dermal margins of exposure (MOEs) do not exceed HED's level of concern (LOC) (i.e., MOEs are $\geq$ 100). In the 2012 risk assessment, the dermal post-application exposure and risks were assessed for adults and children 1 to < 2 years old. Oral post-application exposure via hand-to-mouth activity and associated risk estimates were also assessed for children 1 to < 2

years old. The residential post-application MOEs do not exceed HED's LOC for all scenarios (i.e., MOEs ≥ 100). These assessments assumed 100% of the exposure was to a liquid form. However, recent analyses have shown that the percentage of the exposure to a pet collars resulting from a dust form has the potential to significantly impact the estimated risks. That is, residential post-application risks increase (MOEs are reduced) when a higher percentage of exposures from the pet collar is assumed to be a dust versus a liquid, which underlies the need for additional data as discussed above.

A quantitative spray drift or volatilization assessment will not be conducted during the Registration Review process for flumethrin because the registered use patterns as a treatment on cats and dogs do not result in a significant exposure from spray drift or volatilization.

The occupational exposure database is adequate to support the Registration Review process for flumethrin. In the 2012 risk assessment, the occupational handler exposure and risk estimates were expected to be less than, or at worst case equal to, the residential handler exposures, as this is traditionally considered a consumer product as opposed to one applied by veterinarians or professional groomers. As a result, no quantitative occupational handler exposure and risk assessment was performed. The updated residential handler exposure and risk assessment will be protective for any potential occupational handler exposures and risks. Occupational post-application exposure could potentially occur; however, these types of exposures are not expected to be greater than residential post-application exposures (i.e., minimal and infrequent contact by a professional animal care worker is expected to occur after a collar is applied). As a result, no quantitative occupational post-application exposure and risk assessment was performed. The updated residential post-application exposure and risk assessment will be protective for any potential occupational post-application exposures and risks.

1.0 Introduction

Flumethrin, cyano(4-fluoro-3-phenoxyphenyl)methyl 3-[2-chloro-2-(4-chlorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate, is a synthetic pyrethroid insecticide. Flumethrin is registered for the control of ticks, lice, and mites for use in cat and dog collars that also contain imidacloprid. This scoping document addresses only the active ingredient flumethrin. There are two different sizes of collars currently registered for flumethrin, both of which contain 4.5% flumethrin and 10% imidacloprid. The collars have an efficacious life of 8 months. The small collar weighs 12.5 grams and is intended for use on cats and small dogs up to 8 kg in weight. The large collar weighs 45 grams and is intended for use of dogs over 8 kg in weight. There are restrictions on the label preventing the use of collars on puppies under 7 weeks of age or kittens under 10 weeks of age. There are no other registered or proposed uses of flumethrin. The most recent human health risk assessment was conducted in 2012 (Memo, C. Smith, *et al.*, 6-MAR-2012; D392125).

2.0 Hazard Characterization/Assessment

The toxicology database for flumethrin is sufficient to assess risk for non-food uses. The database of experimental toxicology studies available for flumethrin provides a robust characterization of the hazard potential for children 6 years old and older and for adults. There are no outstanding studies according to Part 158 data requirements for a non-food use pesticide registration. However, there are on-going efforts to develop data to inform the potential sensitivity of infants and younger children to pyrethroids as a class. Despite these scientific

efforts, HED is confident that points of departure and uncertainty factors can be chosen for risk assessment which are health protective and have a strong scientific foundation. The TOXLINE (National Library of Medicine) database literature search did not identify any new toxicological information not already considered.

Flumethrin is a Type II pyrethroid and as such, neurobehavioral changes characteristic of these chemicals (e.g., pawing, burrowing, salivation, and coarse tremors leading to choreoathetosis (CS-syndrome) as well as decreased motor activity) were observed in experimental toxicology studies with flumethrin in all species and durations. However, decreased motor activity occurred at lower doses than other neurobehavioral changes and is considered the most sensitive effect. Flumethrin also produced decreased body weights, and food consumption in repeat dosing studies at similar doses that produced decreased motor activity.

Although offspring and developmental effects were reported in the reproduction and developmental toxicity studies, respectively, these occurred in the presence of parental toxicity. In turn, parental toxicity occurred at doses at least two times higher than the doses eliciting decreased motor activity. Thus, no evidence of increased quantitative or qualitative susceptibility was observed in the flumethrin database. However, in the extensive scientific literature for pyrethroids, there is evidence of increased quantitative susceptibility related to pyrethroid pharmacokinetics. Based on this susceptibility, the agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age.

Flumethrin is not immunotoxic and it is not mutagenic in bacteria or in cultured mammalian cells. Flumethrin is classified as "not likely to be carcinogenic to humans" based on the lack of evidence of carcinogenicity in chronic studies in mice and rats.

The pharmacokinetics of flumethrin is similar to other pyrethroids (i.e., rapid absorption and clearance). Following a single oral dose, flumethrin was excreted mainly via the feces (68%) within 24 hours. In radiolabeled flumethrin studies, absorbed radioactivity calculated as the sum of urine, bile and body tissues accounts for 75% of the given dose in bile duct-cannulated rats, indicating a high level of absorption following an oral dose. The rapid absorption was also observed in an exploratory pharmacokinetic (PK) study where the maximum plasma levels of flumethrin were found at two and four hours after administration for each dose level, respectively.

The acute toxicity profile of flumethrin consists of mild toxicity via the oral, dermal, and inhalation routes of exposure (Toxicity Category II). The eye irritation study indicates that the technical is an amorphous glass-like solid that does not exist as a fine powder at room temperature and so cannot be tested by this exposure route. A waiver was granted for the eye irritation study with assignment to Toxicity Category IV by this exposure route. Flumethrin was assigned to Toxicity Category IV as a skin irritant and it is not a dermal sensitizer.

Conclusions for Hazard Identification/Toxicology:
The toxicology database for flumethrin is sufficient to assess risk for non-food uses. As part of Registration Review, the endpoints, doses, and uncertainty/safety factors most recently selected may be re-evaluated according to the most up-to-date HED policy.

3.0 Residue Chemistry

There are no proposed or currently registered food uses for flumethrin; therefore, residue chemistry data are not required for flumethrin at this time.

4.0 Dietary Exposure

A dietary (food and drinking water) exposure assessment is not required since there are no proposed or currently registered food uses for flumethrin and drinking water exposure is not expected from the registered uses.

5.0 Residential Exposure

Residential handler exposures to the registered flumethrin pet collars may occur via the dermal route while the collars are placed on a cat or dog. As a result, a dermal residential handler exposure assessment was performed for homeowners applying the collar to a cat or dog. Additionally, residential post-application exposures to flumethrin can also occur after collars are placed on a cat or dog via dermal and oral exposure routes.

Residential Handler

In the 2012 risk assessment, the residential handler exposure and risk estimates indicate that the dermal MOEs do not exceed HED's level of concern (LOC) (i.e., MOEs are ≥ 100) (Memo, C. Smith, *et al.*, 6-MAR-2012; D392125).

Residential Post-Application

In the 2012 risk assessment, the dermal post-application exposure and risk estimates were assessed for adults and children 1 to < 2 years old and oral (hand-to-mouth) post-application exposure and risk estimates were assessed for children 1 to < 2 years old. The residential post-application MOEs do not exceed HED's LOC for all scenarios (i.e., MOEs ≥ 100) (Memo, C. Smith, *et al.*, 6-MAR-2012; D392125).

It should be noted that a pet transferable residue study (i.e., a petting study) was not submitted for flumethrin. Bayer did submit chemical-specific data (MRID 48240140 (Dosage of the Imadicloprid 10% Flumethrin 4.5% Collar and Release of the Active Ingredients Over Time in Cats and Dogs, Review Compilation) provides a summary of all of the data) related to the amount of flumethrin that was released from the small and large collars over the life of the collar (i.e., 8 months or 240 days). Depending on the dosage study, measurements were taken at 30, 60, 90, and 240 days after applying the collar and these studies were performed on cats (small collars) and dogs (large collars). These data do not specifically provide the surface residues of flumethrin on a cat or dog, nor do they provide the amount of flumethrin that could be transferred to a person who contacts a treated cat or dog or what formulation type (liquid or solid) is present. Since acute exposures are most toxicologically relevant for flumethrin, HED is most interested in flumethrin residues for the first few days after the collar is applied. The available studies did not collect any data from these days, so for the 2012 assessment, HED focused only on the data that was collected at 30 days as the release rates for flumethrin for both the small and large collar.

Recently, NRDC has questioned the potential for exposure to the dust form of a chemical from the use of impregnated pet collars. The 2012 Residential SOPs currently assume all exposure from pet collars is analogous to exposure to a liquid. As a result of NRDC's question, the agency has started efforts to re-evaluate pet collars to carefully consider whether exposure to pet collar products are more closely related to more traditional liquid formulation pet products such as shampoos and spot-ons, solid formulated products such as dusts and powders, or some combination of both. The agency intends to request and review additional information relating to this issue for all registered pet collar products as they go through the Registration Review process, as well as any proposed new pet collar uses. This evaluation will continue until the agency is satisfied that, based on the design and operation of pet collar products, the exposure from pet collars is understood. This will enable the agency to more accurately make recommendations for human health risk assessment of exposures from the use of pet collars.

The agency recently requested that the flumethrin registrants provide further information relating to the design or manufacturing of the pet collar product to better understand how it acts on the treated animal, including any information relating to whether a liquid or dust is present once the pet collar is applied, and in what form the active ingredients are released and distributed on the treated animal. The registrant's response to the request involved a white paper discussion of the Seresto pet collar distribution/release information as well as the recommendation that the flumethrin product be assessed as a liquid. The registrant's rationale included a statement that, "Even though the collars may release the insecticides to the surface of the collar as a liquid, solid, or semi-solid, the insecticides are continuously wiped from the collar onto the dog's hair and skin and dispersed along the animal's body as a solution or suspension in the natural oils of the animal's skin. Therefore, the exposure of humans to the active ingredients of the Seresto collar is through contact with the oil of the dog's skin." Based on the distribution/release information and other rationale, the agency agrees with the registrant about the information relating to the physical properties of the active ingredient and the likely mechanism of delivery of flumethrin. However, the agency still has questions about the physical forms that are present on the surface of the collar and on the treated pet. The white paper did not present any information or data to directly address this question.

Without specific information or data, the agency is not able to determine if flumethrin should be assessed as a liquid, dust, or some combination of the two. Therefore, the agency is requesting additional information to inform the risk assessment for post-application residential exposure. The agency will work with the registrant to determine the exact data that can answer this question. A traditional pet transferable residue study (i.e., a petting study) or other study that would inform the agency's risk assessment is required.

Conclusions for Residential Exposure:
The residential exposure database is not adequate to support the Registration Review process for flumethrin. As part of Registration Review, the agency will be reassessing the exposures from the use of pet collars. Previous assessments have considered exposures to flumethrin from the pet collars to be in the liquid form; however, recently, the agency has questioned whether exposure from pet collars is a liquid form, solid form, or some combination of both which dictates how exposures are calculated. As a result, the agency is seeking information from the registrant on the relative amounts of solids (e.g., dust) or liquids available for exposure as a result of the use of flumethrin-impregnated pet collars. The agency is requesting additional information to inform the risk assessment for post-application residential exposure and plans to work with the registrant to determine the exposure data that can answer this question. A

traditional pet transferable residue study or some other study that would inform the agency's risk assessment is required. Therefore, an updated residential post-application exposure assessment will be required during Registration Review based upon HED's Residential SOPs, any potential updates to the toxicological PODs, and/or the additional required data received by the agency that affects exposure estimates.

6.0 Non-occupational and Bystander Exposure

A quantitative spray drift or volatilization assessment will not be conducted during the Registration Review process because the registered use patterns as a treatment on cats and dogs do not result in a significant exposure from spray drift or volatilization.

7.0 Aggregate Risk Assessment

There are currently no registered food uses for flumethrin and drinking water exposures are not expected from the registered pet collar uses of flumethrin; therefore, a quantitative aggregate risk assessment is not required at this time.

8.0 Occupational Exposure

Based on the registered flumethrin pet collar uses, there is potential for both occupational handler and occupational post-application exposure to occur. In the 2012 risk assessment, HED assumed that the registered pet collars are mainly directed toward homeowner use.

Occupational Handlers

For the flumethrin pet collar uses, the occupational handler exposures are expected to be less or at worst case equal to the residential handler exposures as this is traditionally considered a consumer product as opposed to one applied by veterinarians or professional groomers. As a result, no quantitative occupational handler exposure and risk assessment was performed. The updated residential handler exposure and risk assessment will be protective for any potential occupational handler exposures and risks.

Occupational Post-Application

For the flumethrin pet collar uses, occupational post-application exposure could potentially occur; however, these types of exposures are not expected to be greater than residential post-application exposures (i.e., minimal and infrequent contact by a professional animal care worker is expected to occur after a collar is applied). As a result, a quantitative occupational post-application exposure and risk assessment has not been performed. The updated residential post-application exposure and risk assessment will be protective for any potential occupational post-application exposures and risks.

Conclusions for Occupational Exposure:
The occupational exposure database is adequate to support the Registration Review process for flumethrin. A quantitative occupational handler exposure and risk assessment may not be conducted during Registration Review. The updated residential handler exposure and risk assessment will be protective for any potential occupational handler exposures and risks. A

quantitative occupational post-application exposure and risk assessment may not be conducted during Registration Review. The updated residential post-application exposure and risk assessment will be protective for any potential occupational post-application exposures and risks.

9.0 Public Health and Pesticide Epidemiology Data

For this evaluation, the OPP Incident Data System (IDS), the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR), and the National Pesticide Information Center (NPIC) databases were consulted for pesticide incident data on the active ingredient flumethrin (PC Code: 036007). The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to flumethrin exposure. Flumethrin is not included in the Agricultural Health Study (AHS) and therefore this study does not provide information for this report.

For the Main IDS, from January 1, 2012 to February 4, 2016, there were 137 flumethrin incidents reported in the database. Thirteen of these incidents were classified as major severity and 124 incidents were classified as moderate severity. For major severity incidents, dermal symptoms were reported most often including rash, pruritus and burning sensation. The major severity incident narratives are summarized Memo, S. Recore, *et al.*, pending; D435503.

In Aggregate IDS, from January 1, 2012 to February 4, 2016, there were 219 incidents reported involving flumethrin. These incidents were classified as minor severity.

A query of SENSOR-Pesticides from 1998-2012 identifies no cases involving flumethrin. This product (Registration No. 11556-155) was registered in 2012 and therefore incident data were not likely to be available in the current SENSOR-Pesticide dataset.

From January 1, 2011 to December 31, 2015, one human incident involving flumethrin was reported to NPIC. This incident was classified as minor severity and possibly related to use of the product (Registration No. 11556-155). An adult female applied the collar to her 90 pound Yellow Labrador. She reported that sometimes her hands burn after she had been petting the dog.

Due to the fact that the only flumethrin end use product (Seresto Collar, Registration No. 11556-155) is a relatively new product that was registered on March 16, 2012, the agency will continue to monitor the incident data and if a concern is triggered, additional analyses will be conducted.

10.0 Tolerance Assessment and International Harmonization

There are no established or proposed tolerances for flumethrin in or on any food or feed crops; therefore, harmonization is not an issue at this time.

11.0 Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in the most recent flumethrin human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-

Income Populations[8]." The OPP typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

12.0 Cumulative

The agency is required to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The agency has determined that the pyrethroids and pyrethrins share a common mechanism group (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). The members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. The cumulative risk assessment for the pyrethroids/pyrethrins was published on Nov. 9, 2011 (USEPA, 2011a) and is available at http://www.regulations.gov; EPA-HQ-OPP-2011-0746. No cumulative risks of concern were identified allowing the agency to consider new uses for pyrethroid actives. For information regarding EPA's efforts to evaluate the risk of exposure to pyrethroids, refer to http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.

Since HED completed its first risk assessment for flumethrin in 2012, flumethrin was not included in the initial common mechanism grouping (CMG) science policy document from 2008 and was not assessed in the November 2011 pyrethroid cumulative risk assessment. However, the agency has determined based on its chemical structure and based on the observation of neurobehavioral effects consistent with Type II pyrethroids, that flumethrin should be included in the CMG for this class of pesticides. As such, the agency must consider the potential contribution of flumethrin to the cumulative risk assessment. As part of the 2012 assessment for the flumethrin pet collar uses, the agency performed a quantitative analysis and determined that the proposed flumethrin pet collar use will not significantly contribute to or change the overall findings in the pyrethroid cumulative risk assessment.

13.0 Human Studies

Past flumethrin risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal exposure; particularly data included in the Pet SOP from the 2012 Residential SOPs. EPA has reviewed all the studies supporting the SOPs and found no clear and convincing evidence that the conduct of any of them was either fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted. All applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied, and there is no regulatory barrier to continued reliance on these studies.

14.0 Risk Assessment Updates and Data Deficiencies

EPA notes the following risk assessment updates and data deficiencies will need to be completed and addressed during Registration Review:

[8] http://www.epa.gov/compliance/environmentaljustice/resources/policy/exec_order_12898.pdf

- Toxicology:
  - None.
- Residue Chemistry/Dietary Exposure:
  - None.
- Occupational/Residential Exposure:
  - The agency is seeking information from the registrant on the relative amounts of dust versus liquid available for exposure as a result of the use of flumethrin-impregnated pet collars. The agency is requesting additional information to inform the risk assessment for post-application residential exposure and plans to work with the registrant to determine the exact data that can answer this question. A traditional pet transferable residue study (*i.e.*, a petting study) or other study that would inform the agency's risk assessment is requested.

15.0 References

Memoranda Relevant to Registration Review.			
Author	Barcode	Date	Title
C. Smith, et *al.*	D392125	March 6, 2012	Flumethrin: Human Health Risk Assessment for the Section 3 Registration Action for Cat and Dog Collars
S. Recore, *et al.*	D435503	Pending	Flumethrin: Tier I Review of Human Incidents for Draft Risk Assessment

Attachments:

Attachment 1: Chemical Identity Tables.
Attachment 2: Flumethrin Acute, Subchronic, and Chronic Toxicity Profile.
Attachment 3: Summary of Toxicological Doses and Endpoints for Flumethrin.
Attachment 4: Summary of Registered Uses for Flumethrin.

Attachment 1: Chemical Identity Tables.

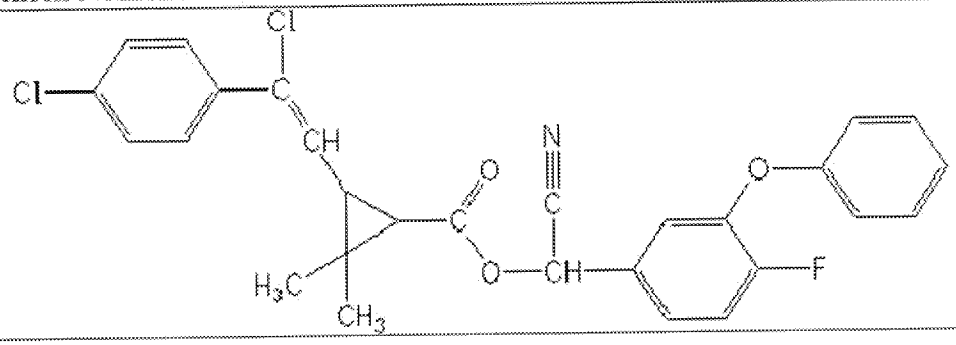
Table A.1.1: Flumethrin Nomenclature	
Chemical Structure	
Common Name	Flumethrin
IUPAC name	(*RS*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-(*EZ*)-3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate
CAS Name	cyano(4-fluoro-3-phenoxyphenyl)methyl 3-[2-chloro-2-(4-chlorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate
CAS Registry Number	69770-45-2
Chemical Class	Synthetic pyrethroid

Table A.1.2: Flumethrin Physical and Chemical Properties	
Parameter	**Value**
Molecular Weight	510.4 g/mol.
Boiling Point	>250°C
Water solubility (20°C)	9.7×10^{-5} mg/l
Solvent solubility (20°C)	No Data
Vapor pressure (25°C)	3.9×10^{-9} mm Hg
Henry's Law Constant (25°C)	4.2×10^{-8} atm-m^3/mol
Octanol/water partition coefficient	log Kow = 7.65

Attachment 2: Flumethrin Acute, Subchronic, and Chronic Toxicity Profile.

A.1 Toxicology Data Requirements

Guideline Number and Toxicity Study		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	no
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Sub-chronic (Rodent)	CR	yes
870.3150	Oral Sub-chronic (Non-Rodent)	CR	no
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	yes	yes
870.3465	90/28-Day Inhalation	CR	yes
870.3700	Developmental Toxicity (Rodent)	yes	yes
870.3700	Developmental Toxicity (Non-rodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100	Chronic Toxicity (Rodent)	CR	no
870.4100	Chronic Toxicity (Non-rodent)	no	yes
870.4200	Oncogenicity (Rat)	CR	no
870.4200	Oncogenicity (Mouse)	CR	yes
870.4300	Chronic/Oncogenicity	CR	yes
870.5100	Mutagenicity: Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity: Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity: Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity: Structural Chromosomal Aberrations	yes	yes
870.5500	Mutagenicity: Other Genotoxic Effects	yes	yes
870.5550	Mutagenicity: Other Genotoxic Effects	yes	no
870.6100	Acute Delayed Neurotoxicity (Hen)	CR	--
870.6100	90-Day Neurotoxicity (Hen)	CR	--
870.6200	Acute Neurotoxicity Screening Battery (Rat)	yes	yes
870.6200	90 Day Neuro. Screening Battery (Rat)	yes	yes
870.6300	Developmental Neurotoxicity	CR	yes
870.7485	General Metabolism	CR	yes
870.7600	Dermal Penetration	CR	no
870.7800	Immunotoxicity	yes	yes

--Not applicable

Appendix A.2 Toxicity Profiles

Table A.2.1: Acute Toxicity Profile – Flumethrin (PC 036007)

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral, rat	48240203	LD_{50} Females = 175 mg/kg	II
870.1100	Acute oral, rat	48240204	LD_{50} Males > 100 mg/kg LD_{50} Females = 100 mg/kg	II
870.1200	Acute dermal, rat	48240206	LD_{50} Males = 1998 mg/kg LD_{50} Females = 1436 mg/kg	II
870.1300	Acute inhalation, rat	48240208	LC_{50} Males > 0.585 / <0.812 mg/L LC_{50} Females > 0.277 / <0.585 mg/L	II
870.2400	Acute eye irritation, rabbit	48240211	Waiver requested	IV
870.2500	Acute dermal irritation, rabbit	48240213	Slight irritant; PII=0.25 Bruising observed one animal at 1 hr.	IV
870.2600	Skin sensitization, guinea pig	48240107	Formulation PNR1427 (4.35% flumethrin) is not s sensitizer	No applicable

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin

Guideline No.	Study Type	MRID No. (year)/ Classification/ Doses	Results
870.3100	Subchronic (Oral) Toxicity - Rodent	48240222 (1995) rat Acceptable/guideline 0, 10, 40, 160 ppm (rat) M: 0, 0.7, 2.9, or 11.9 mg/kg/day F: 0, 0.8, 3.4, 13.0 mg/kg/day	NOAEL- 0.7/0.8 mg/kg/day (M/F) LOAEL – 2.9/3.4 mg/kg/day (M/F), ↑extramedullary hematopoiesis; ↓hemosiderin storage; labored breathing; ↑salivation (F); shoulder wounds (M)
		48240224 (1998) mice Acceptable/guideline (mice) 0, 5, 10, **60, 120, 240, 480** ppm **(95.1%, T0059204)** M: 0, 9.9, 20.8, 42.2 mg/kg/day F: 0, 13.2, 26.5, 56.0 mg/kg/day (94.4%, T4060297) M: 0, 0.9, 1.9 mg/kg/day F: 0, 1.4, 2.5 mg/kg/day	NOAEL - 0.9/1.9 (M/F) LOAEL - 1.4/2.5 mg/kg/day, piloerection, dermal lesions, mild hyperkeratosis and acanthosis, emaciation, and mortality at higher doses

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin

Guideline No.	Study Type	MRID No. (year)/ Classification/ Doses	Results
870.3250	90 Day Dermal Toxicity - Rat	48240216 (2008) Acceptable/guideline 0, 10, 30, or 80 mg/kg/day	NOAEL - 10 mg/kg/day LOAEL - 30 mg/kg/day, loss of hair; ↓BW and ↓BWG (M), ↓erythrocytes, high stepping gait, ↓ABS spleen wt
870.3200	28 Day Dermal Toxicity - Rat	48240217 (2006) Acceptable/non-guideline 0, 100, 150, 200 mg/kg/day	NOAEL – not established, insufficient number of animals. Clinical signs: bloody muzzle, sunken flanks, reduced motility, high-stepping gait, labored breathing, diarrhea, narrowed eyelids, ↑salivation
	14 Day Dermal Toxicity - Rat	48240218 (2007) Acceptable/non-guideline 0, 10, 30, 100 mg/kg/day	NOAEL – not established, insufficient number of animals. Clinical signs: bloody muzzles, bleedings on nose, hunched backs, reduced motility, high-stepping gait, labored breathing, narrowed eyelids, ↑salivation
870.3700a	Prenatal Developmental Toxicity - Rat	48240225 (1999) Acceptable/guideline 0, 0.75, 2, 5 mg/kg/day	**Maternal** NOAEL – 0.75 mg/kg/day. LOAEL - 2 mg/kg/day, ↓ *H2O, ↓feces, ↓BW/BWG, ↓gravid uterine wt, ↓food consumption*; ↓BW **Developmental** NOAEL – 2 mg/kg/day. LOAEL - 5 mg/kg/day, ↓BW , ↓placenta wt retardation/ossification/microphthalmia
870.3700b	Prenatal Developmental Toxicity – (Rabbit)	48240226 (2009) Acceptable/guideline 0, 0.5, 1.5, 4.5 mg/kg/day	**Maternal** NOAEL – 1.5 mg/kg/day. LOAEL – 4.5 mg/kg/day, Abortions, cold ears, hind limb swelling, soft feces, ↓H2O, ↓urine, enlarged gall bladder, encrusted wounds at throat/forelimbs **Fetal** NOAEL – 1.5 mg/kg/day. LOAEL – 4.5, retarded ossification of metacarpals, phalanges, 1st cervical vertebrae
870.3800	Reproduction and Fertility Effects	48240227 (2008) 0, 0.5, 1, 3 mg/kg/day Acceptable/guideline Gavage	**Parental** NOAEL not established (M) LOAEL - 0.5 mg/kg/day ↓pituitary in F1 (15%) NOAEL - 0.5 (F) LOAEL - 1.0 mg/kg/day ↓liver weights in F0 & F1 **Reproductive** NOAEL - 3.0 mg/kg/day HDT **Offspring** NOAEL - 1.0 mg/kg/day M/F LOAEL - 3.0 mg/kg/day thinness, no milk spots, ↓BW, ↓rearing indexes with ↑deaths at PND 0-4.

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin

Guideline No.	Study Type	MRID No. (year)/ Classification/ Doses	Results
		48240228 (1992) Acceptable/guideline 0, 1, 5, 50 ppm M: 0, 0.05, 0.23, 2.42 mg/kg/day F: 0, 0.06, 0.28, 2.92 mg/kg/day Dietary	**Parental** NOAEL = 0.23 mg/kg LOAEL = 2.42 mg/kg ↓body weight gain in P generation (males), ↓body weight and food consumption in (females) during lactation, ↑postnatal loss in all generations, ↓food consumption in P and F1 males, ↓body weight gain in male and female pups in all generations **Reproductive** NOAEL = 2.42 mg/kg HDT **Offspring** NOAEL = 0.23 mg/kg. LOAEL = 2.42 mg/kg ↓body weight and body weight gains in males and female pups, significantly different testes and ovaries weight, ↓ survival at 21 days
870.3465	Inhalation Toxicity	48240219 (1997) Acceptable/guideline 0.1, 1.4, 20.0 mg/m^3 Analytical 0.12, 1.33 and 22.4 mg/m^3	NOAEL = 0.12 mg/m^3 LOAEL = 1.33 mg /m^3 based on clinical signs of neurotoxicity (bradypnea, labored breathing, red discharge or encrustations from the perinasal area, decreased motility, atony and salivation).
870.4200	Carcinogenicity - Mouse	48240223 (1999) Acceptable/guideline 0, 1,3, 15, 30 ppm M: 0, 0.12, 0.39, 1.97, 4.56 mg/kg/day F: 0, 0.15, 0.52, 2.54, 4.95 mg/kg/day	NOAEL = 0.39/0.52 (M/F) mg/kg/day LOAEL = 1.97/2.54 (M/F) mg/kg/day, ↑skin discoloration, incrustations, sores, missing/deformed ears, epidermal hyperplasia, inflammation, ulceration, M= enlarged/swollen spleens, ↑plasmacytosis mandibular LN, hematopoiesis BM, ↑reduced liver glycogen and hepatocytic atrophy (salivation seen at higher doses, 60ppm↑) There were no increased incidences of treatment related tumors compared to controls
870.4300	Combined Chronic Toxicity/ Carcinogenicity - Rat	42820221 (1999) Acceptable/guideline 0, 0.7, 2, 4 mg/kg/day	NOAEL = 0.7 mg/kg/day LOAEL = 2 mg/kg/day Severe skin lesions, enlarged LN/swollen spleens, plasmacytosis, ↑adrenal cortex vacuolation, no treatment related tumor incidence compared to controls
870.6200a	Neurotoxicity Screening Battery - Acute - Rat	48240215 (2008) Acceptable/guideline 0, **0.25, 0.50**, 1, 5, 15 mg/kg	NOAEL = 0.5 mg/kg/day in **males** LOAEL = 1.0 (M/F) mg/kg/day, ↓motor/locomotor activity, ↑staining of mouth, perianal, nose, ↑lacrimation, salivation at ↑doses

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.6200b	Neurotoxicity Screening Battery - Subchronic - Rat	48240220 (2008) Acceptable/ guideline 0, 1, 2.5, 5 mg/kg/day	NOAEL – 1 mg/kg/day LOAEL – 2.6 mg/kg/day, ↓food consumption, BW/BWG males only, urine/lacrimal/perianal/oral stains, ↓figure8 maze activity (Salivation seen at higher doses)
870.6300	Neurotoxicity Developmental	48240232 (2008) Acceptable/guideline 0, 0.5, 1, 2 mg/kg/day	**Maternal** NOAEL – 1 mg/kg/day LOAEL- 2 mg/kg, BW/day for maternal animals and offspring, based on ↓body weight (-3%) and body weight gain (-9%, $p<0.05$), and ↓food consumption (-15%, $p<0.05$, in dams only). Salivation also seen. **Offspring** NOAEL – 1mg/kg/day LOAEL- 2 mg/kg, ↓ BW in M on PND 11 and 17 (- 8%, $p<0.01$) and in the low and high dose F on PND 11 (-6%, $p<0.05$) and were associated with significant reduced body weight gain that began on PND 4-11. In addition, body weight was non-statistically decreased on PND 21 in M. This difference in body weight for males persisted to study termination (statistically decreased 6-7% compared to control).
870.5100	Bacterial Reverse Mutation Test	48240233 (1993) Acceptable/guideline 0, 8, 40, 200, 1000, and 5000 µg/plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240234 (1993) Unacceptable/non-guideline 0, 7500, 10,000, 12,500, 15,000 µg/plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240235 (2006) Acceptable/guideline 0, 16, 50, 158, 500, 1581 and 5000 ug/per plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.5300	In vitro mammalian cell gene mutation test	48240236 (1995) Acceptable/guideline 0, 6.25, 12.5, 25, 50, 75, and 100 µg/mL (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240237 (2007) Acceptable/guideline 0, 25, 50, or 100 µg/mL	There was no evidence of chromosomal aberrations. [Negative]
		48240239 (2007) Acceptable/guideline 0, 6, 12, 24, 48, 96 or 182 µg/mL	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5375	In vitro mammalian chromosome aberration test	48240238 (1995) Acceptable/guideline 100, 200, 500, 1000, 2500, or 5000 µg/mL (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5395	Mammalian erythrocyte micronucleus test	48240240 (2007) Acceptable/guideline 0, 125, 250, 500 mg/kg	This chemical was not found to be clastogenic or aneugenic. [Negative]
		48240241 (1995) Acceptable/guideline 0, 1000mg/kg	There was no evidence of chromosomal aberrations with or without activation. [Negative]
870.5500	Unscheduled DNA Synthesis *in vitro*	48240242 (1994) Acceptable/guideline 0, 5, 10, 50, 100, 200, 300, 500 µg/mL	There was no evidence of genotoxic activity. [Negative]

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.7485	Metabolism and pharmacokinetics	48240243 (1992) Acceptable/guideline 1, 5 mg/kg	Radioactivity administered with [Cl-phenyl-U-^{14}C] flumethrin was rapidly but incompletely absorbed from the intestinal lumen of rats. Excretion of the compound was slow and mostly in the feces comprising 77-88 % of the dose. The majority of the radioactive feces eliminated had been absorbed and excreted with the bile into the gut lumen. The highest amount of radioactivity in the body was mainly found in the plasma, which at sacrifice showed the highest residue concentration in dose groups tested. All other organs exhibited significantly lower concentrations. The lowest values were determined in the brain, indicating that the blood-brain barrier is almost impermeable for the test compound and its labeled metabolites. The radioactive residues in the body excluding the gastrointestinal tract at sacrifice, seven days after dosing, were still relatively high, varying between 9 % and 20 % of the given dose. The multiple dose experiment clearly showed an accumulation of the radioactivity in the body. The 24 hour dosing interval was too short to completely allow for the elimination of the administered radioactivity. Since the renal excretion played only a negligible role, metabolite identification was conducted exclusively in the feces.
		48240244 (2000) Acceptable/non-guideline 0, 50, 160ppm	Mean plasma concentration of flumethrin and flumethrin granules after 3, 6, 13 weeks of 160ppm were bioavailability were similar
870.7800	Immunotoxicity	48240250 (2009) Acceptable/guideline 0, 10, 40, 160 ppm 0, 0.8, 3, 11.7 mg/kg/day M 0, 1, 3.5, 12.3 mg/kg/day F	Systemic NOAEL- 3/3.5 LOAEL-11.7/12.3 (M/F) ↓BW (significant in week 1 only for F)
Non-guideline	4-week Gavage Pilot. for 2-Gen rat repro	48240229 (2006) Acceptable/non-guideline 5.0, 7.5,10.0 mg/kg/day	Males NOAEL- Not established. LOAEL = 5 mg/kg/day (HDT) ↓reduced mean relative spleen and thymus weights and ↓absolute thymus and spleen weight. Females LOAEL - 10 mg/kg/day slightly ↓ mean body weight and reduced mean absolute and spleen weights Female NOAEL = 7.5 mg/kg/day

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
Non-guideline	Rat Plasma – Gavage, 2 –Gen rat repro	48240245 (2007) Acceptable/non-guideline 0, 0.5, 1.0, or 3.0 mg/kg/day	Plasma concentration study, a part of the 2-generation reproduction study no. (MRID 48240227). The animals were grouped into one control and 3 dose groups per sex and generation. All results for control group animals were below the limit of quantification. Results obtained from rats in the various dose groups showed a clear dose-concentration relation. The highest concentrations were found four hours after dosing. The concentration results for male animals were significant higher than for females.
Non-guideline	Rat Plasma – Pilot with MRID 48240230	48240231 (2006) Acceptable/non-guideline 0.08, 0.4 or 2 mg/kg/day	This study was part of an exploratory subchronic oral toxicity study (MRID 48240230) in which plasma was collected from male and female rats and analyzed to determine plasma concentrations of flumethrin. Maximum plasma levels were measured at 2 to 4 hours after administration at each dose level. At the dose concentration between 0.4 and 2.0 mg/kg there was a clear increase of plasma levels with dose that was visible in both sexes. Continuing plasma level increases were not seen in the dosage range of 3.0 to 5.0 mg/kg (after enhanced dose scheme).
Non-guideline	19-week Gavage Pilot, for 2-Gen rat repro	48240230 (2006) Acceptable/non-guideline 0, 0.08, 0.4, 2.0 mg/kg/day After day 70: 3, 4, 5 mg/kg/day	**Parental male** NOAEL- 3 mg/kg/day LOAEL - 4 mg/kg/day ↓slightly body weight. **Parental female** NOAEL - 2 mg/kg/day lack of effects prior to dose elevation LOAEL- 3 mg/kg/day ↓bw during pregnancy. **Offspring** NOAEL –2 mg/kg/day LOAEL = 3 mg/kg/day The body weight changes were insignificant for M/F. ↑absolute adrenal wt in F ($p<0.01$) and ↓thymus weight in males- 3, 4 mg/kg/day.

Attachment 3: Summary of Toxicological Doses and Endpoints for Flumethrin

Table 4.5.4: Summary of Toxicological Doses and Endpoints for Flumethrin*

Exposure Scenario	Dose Used in Risk Assessment, UF	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Incidental Oral Short-Term (1-30 days)	NOAEL= 0.5 mg/kg/day	UF_A = 10x UF_H = 10x, FQPA/UFqs = 3x	Residential LOC for individuals < 6 years old = 300	Acute Neurotoxicity Study MIRD 48240215 LOAEL= 1 mg/kg/day in males based on ↓motor/locomotor activity, ↑staining of mouth, perianal, nose, ↑lacrimation, salivation at ↑doses
Dermal Short-term (1-30 days) (< 6 years old)	NOAEL = 10 mg/kg/day	UF_A = 10x UF_H = 10x FQPA/UFqs = 3x	Residential LOC for MOE = 300	90-day Dermal Study MIRD 48240216 LOAEL=30 mg/kg/day Based on loss of hair; ↓BW and ↓BWG (M), ↓erythrocytes, high stepping gait, ↓ABS spleen wt.
Dermal Short-term (1-30 days) (≥ 6 years old)	NOAEL = 10 mg/kg/day	UF_A = 10x UF_H = 10x FQPA/UFqs = 1x	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	90-day Dermal Study MIRD 48240216 LOAEL=30 mg/kg/day Based on loss of hair; ↓BW and ↓BWG (M), ↓erythrocytes, high stepping gait, ↓ABS spleen wt.
Inhalation Short-term (1-30 days) (< 6 years old)	NOAEL = 0.1 mg/m^3	UF_A = 3x UF_H = 10x FQPA/UFqs = 3x	Residential LOC for MOE = 100	Subchronic inhalation study MIRD 48240219 LOAEL = 1.33 mg /m^3 based on clinical signs of neurotoxicity (bradypnea, labored breathing, red discharge or encrustations from the perinasal area, decreased motility, atony and salivation).
Inhalation (1-30 days) (≥ 6 years old)	NOAEL = 0.1 mg/m^3	UF_A = 3x UF_H = 10x FQPA/UFqs = 1x	Residential LOC for MOE = 30 Occupational LOC for MOE = 30	Subchronic inhalation study MIRD 48240219 LOAEL = 1.33 mg /m^3 based on clinical signs of neurotoxicity (bradypnea, labored breathing, red discharge or encrustations from the perinasal area, decreased motility, atony and salivation).
Cancer (oral, dermal, inhalation)	**Classification:** "Not likely" to be carcinogenic in humans			

*Endpoints selected in 2015 in anticipation of new uses

Attachment 4: Summary of Registered Uses for Flumethrin

Table A.4. Registered Flumethrin End Use Product.

Use Site		Formulation [EPA Reg. No.]	Application Rate	Use Directions and Limitations
Pet Collar Product				
Small Collar	Small dogs and puppies (7 weeks of age and older and up to 18 lbs body weight)	PNR 1427 Insecticide EPA Reg. No. 11556-155 4.5% flumethrin	0.00124 lb ai/collar (562.50 mg ai)	Do not use on puppies under 7 weeks of age or kittens under 10 weeks of age. The collar should be worn continuously for 8 months and replaced after 8 months for optimal protection.
	Cats and kittens 10 weeks of age and older			
Large Collar	Large dogs and puppies 7 weeks of age and older and above 18 lbs body weight		0.00446 lb ai/collar (2,023 mg ai)	

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: September 7, 2016

SUBJECT: Flumethrin: Tier I Review of Human Incidents and Epidemiology for Draft Risk Assessment

PC Code: 036007
Decision No.: 518360
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
MRID No.: NA

DP Barcode: D435503
Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 69770-45-2
40 CFR: NA

Ver.Apr.08

FROM: Shanna Recore, Industrial Hygienist
Toxicology and Epidemiology Branch
Health Effects Division (7509P)
and
Elizabeth Evans, Environmental Protection Specialist
Toxicology and Epidemiology Branch
Health Effects Division (7509P)

THROUGH: David J. Miller, Acting Branch Chief for David Miller
Toxicology and Epidemiology Branch
Health Effects Division (7509P)

TO: Julie Van Alstine, Risk Assessor
Risk Assessment Branch VI
Health Effects Division (7509P)
and
Bonnie Adler, Chemical Review Manager
Risk Management & Implementation Branch 5
Pesticide Re-evaluation Division (7508P)

Summary and Conclusions

From January 1, 2012 to February 4, 2016, there were was 137 incidents reported to Main IDS and 219 incidents reported to Aggregate IDS involving flumethrin. Thirteen of these incidents were classified as major severity, 124 incidents were classified as moderate severity and 219

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incidents were classified as minor severity. In addition there was one minor severity incident reported to NPIC involving flumethrin, from January 1, 2011 to December 31, 2015.

Due to the fact that the only flumethrin end use product (Seresto Collar, Registration No. 11556-155) is a relatively new product that was registered on March 16, 2012, the Agency will continue to monitor the incident data and if a concern is triggered, additional analysis will be conducted.

Detailed Review

I. ACTION REQUESTED

Flumethrin is being considered under the FQPA-mandated Registration Review program established to review, on a 15 year cycle, pesticides for which a Re-registration Eligibility Decision has been made. One component of the Agency's Registration Review Program is consideration of human incident data. In conjunction with a human health risk assessment based on other data sources, such human incident data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products.

Reports of adverse health effects allegedly due to a specific pesticide exposure (*i.e.*, an "incident") are largely self-reported and therefore, generally speaking, neither exposure to a pesticide or reported symptom (or the connection between the two) is validated or otherwise confirmed. Typically, causation cannot be determined based on incident data. However, incident information can be an important source of feedback to the Agency: incidents of severe outcome, or a suggested pattern or trend among less severe incidents, can signal the Agency to further investigate a particular chemical or product. Observational epidemiology studies relate the risk of disease, *e.g.*, cancer, and exposure to an agent such as a pesticide product in the general population or specific sub-groups like pesticide applicators.

II. BACKGROUND

Flumethrin is a synthetic pyrethroid insecticide. Flumethrin has one end use product (Seresto Collar, Registration No. 11556-155) which was registered by the Agency on March 16, 2012. This product is a cat and dog collar used for flea and tick control that also contains imidacloprid.

For this evaluation, both OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on the active ingredient flumethrin (PC Code: 036007). The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to flumethrin exposure.

III. RESULTS/DISCUSSION

a. IDS (Incident Data System)

OPP's IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6(a)(2) reports from registrants, other federal and state health and environmental agencies, and individual consumers. Since 1992, OPP has compiled these reports in IDS. IDS contains reports from across the U.S. and most incidents have all relevant product information recorded. Reports submitted to the IDS represent anecdotal reports or allegations only, unless otherwise stated in the report.

IDS records incidents in one of two modules: Main IDS and Aggregate IDS:

- Main IDS contains incidents resulting in higher severity outcomes and provides more detail with regard to case specifics. This system stores incident data for death, major and moderate incidents, and it includes information about the location, date and nature of the incident. Main IDS incidents involving only one pesticide are considered to provide more certain information about the potential effects of exposure from the pesticide.

- Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). These are reported by registrants only as counts in what are aggregate summaries.

For the Main IDS, from January 1, 2012 to February 4, 2016, there were was 137 flumethrin incidents reported in the database. Thirteen of these incidents were classified as major severity and 124 incidents were classified as moderate severity. Dermal symptoms were reported most often for the major severity incidents, including rash, pruritus and burning sensation. The major severity incident narratives are summarized in Appendix A, Table 1.

In Aggregate IDS, from January 1, 2012 to February 4, 2016, there were 219 incidents reported involving flumethrin. These incidents were classified as minor severity.

b. SENSOR-Pesticides

The Center for Disease Control's National Institute for Occupational Health (CDC/NIOSH) manages a pesticide surveillance program and database known as SENSOR-Pesticides. This database includes pesticide illness case reports in 12 states from 1998-2012. The participating states for a given year vary depending on state and federal funding for pesticide surveillance. Cases of pesticide-related illnesses are ascertained from a variety of sources, including: reports from local Poison Control Centers, state Department of Labor workers' compensation claims when reported by physicians, reports from State Departments of Agriculture, and physician reports to state Departments of Health. Although both occupational and non-occupational incidents are included in the database, the SENSOR coordinators primarily focus their follow-up case investigation efforts on the occupational pesticide incidents. The state SENSOR coordinator at the Department of Health will follow-up with cases and obtains medical records to

verify symptoms, circumstances surrounding the exposure, severity, and outcome. Using standardized protocol and case definitions, SENSOR coordinators at State Departments of Health enter the incident interview description provided by the case, medical report, physician and patient into the SENSOR data system. All SENSOR-Pesticide cases must report a minimum of two health effects in order to be included in the aggregate database that EPA uses for incident analyses.

A query of SENSOR-Pesticides from 1998-2012 identifies no cases involving flumethrin. This product (Registration No. 11556-155) was registered in 2012 and therefore incident data were not likely to be available in the current SENSOR-Pesticide dataset.

c. National Pesticide Information Center (NPIC)

The National Pesticide Information Center or NPIC is a cooperative effort between Oregon State University and EPA which is funded by EPA to serve as a source of objective, science-based pesticide information and respond to inquiries from the public and to incidents. NPIC functions nationally during weekday business hours through a toll-free telephone number in addition to the internet (www.npic.orst.edu) and email. Similar to Poison Control Centers, NPIC's primary purpose is not to collect incident data, but rather to provide information to inquirers on a wide range of pesticide topics, and direct callers for pesticide incident investigation and emergency treatment. Nevertheless NPIC does collect information about incidents (approximately 4000 incidents per year) from inquirers and records that information in a database. NPIC is a source of national incident information but generally receives fewer reports than IDS. Regardless, if a high frequency is observed in IDS, NPIC provides an additional source of information to see whether there is evidence of consistency across national data sets or possibly duplication and additional information about the same incident(s).

From January 1, 2011 to December 31, 2015, one human incident involving flumethrin was reported to NPIC. This incident was classified as minor severity and possibly related to use of the product (Registration No. 11556-155). An adult female applied the collar to her 90 pound Yellow Labrador. She reported that sometimes her hands burn after she has been petting the dog.

d. Agricultural Health Study (AHS)

The AHS is a high quality, prospective epidemiology study evaluating the link between pesticide use and various health outcomes including cancer. The AHS includes private and commercial pesticide applicators and their spouses. If there are AHS findings relevant to a particular pesticide going through registration review, the Agency will ensure they are considered in the problem formulation/scoping phase of the process and, if appropriate, fully reviewed in the risk assessment phase of the process. The AHS includes information on use of 50 different pesticide active ingredients commonly used in agriculture. Flumethrin is not included in the AHS and therefore this study does not provide information for this report.

IV. CONCLUSION

From January 1, 2012 to February 4, 2016, there were was 137 incidents reported to Main IDS and 219 incidents reported to Aggregate IDS involving flumethrin. Thirteen of these incidents were classified as major severity, 124 incidents were classified as moderate severity and 219 incidents were classified as minor severity. In addition there was one minor severity incident reported to NPIC involving flumethrin, from January 1, 2011 to December 31, 2015.

Due to the fact that the only flumethrin end use product (Seresto Collar, Registration No. 11556-155) is a relatively new product that was registered on March 16, 2012, the Agency will continue to monitor the incident data and if a concern is triggered, additional analysis will be conducted.

Appendix A.

Table 1. Human Major Incidents Reported to Main IDS for Seresto Collars

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Incident Description
025708 - 00001	4/26/2013	HARDWICK, MA	011556-00155	SERESTO LARGE DOG	036007,129099	A 47 year old female in poor condition, with a known medical history of food allergies, Lyme disease, Epstein Barr virus, kidney condition, thyroid cancer survivor, was exposed to an unknown amount of Seresto Large Dog when the she hugged her dog that was wearing a Seresto collar. Approximately one week after application of the collar to the dog, the owner developed a rash on the left side of her neck.
026505 - 00006	8/16/2013	SALISBURY, NC	011556-00155	SERESTO CAT	036007,129099	A 79 year old, female in poor condition, with hypertension, high cholesterol, coronary artery disease and a history of a stroke, placed a Seresto Cat collar around the neck of her feline. Approximately one day following the placement of the collar on the cat, she developed pruritus on the palms of her hands and the bottom of her feet. Upon examination by the dermatologist, a skin scraping was performed and the individual was diagnosed with either dry skin or a fungal infection.
026834 - 00006	4/1/2014	WILKES BARRE, PA	011556-00155	SERESTO DOG (UNSPECIFIED)	036007,129099	A 42 year old female in good condition with eczema was exposed to a Seresto Dog Collar while applying it to the dog. At unknown intervals the human kisses the dog's head. Since the collar has been applied, she gets a bad taste in her mouth (taste alteration) each time she kisses the dog.
027273 - 00005	9/3/2014	NEW SALISBURY, IN	011556-00155	SERESTO DOG	036007,129099	A 71 year old female in good condition with allergies was exposed to a Seresto Cat collar that she placed around the cat's neck. During placement of the collar on the cat, the woman felt a tingling sensation on her fingers. She washed hands with soap and water. Approximately 10 minutes post exposure the collar, the clinical sign stopped. The woman has a skin irritation after she pets the cat.
027357 - 00008	########	WYNANTSKILL, NY	011556-00155	SERESTO SMALL DOG	036007,129099	A 63 year old female in fair condition, with thyroid nodules, placed a Seresto Small Dog collar around the neck of her canine. Approximately 2 hours following the placement of the collar, she developed pain under her left arm. Three days later, she had a seizure, blacked out and could not speak for approximately 15 seconds. Two weeks later she had another seizure. She went to a neurologist for examination. Six weeks following exposure she became lethargic. One month later, her thyroid nodules increased in size. She went to a physician and had a biopsy performed. The results are unknown at this time.
027514 - 00001	4/7/2014	STUART, FL	011556-00155	SERESTO SMALL DOG	036007,129099	A 45 year old, female, in good condition, with allergies, placed a Seresto Small Dog collar around the neck of her dog. Approximately 2 weeks to a month later, she developed a pruritic erythemic rash on her arms. About a month later, she went to a dermatologist and was prescribed oral prednisone and an unknown topical cream. Nine month later, she went

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Incident Description
						the dermatologist and had a core biopsy performed which revealed lichenoid dermatitis.
027771 - 00005	2/28/2015	EADS, TN	011556-00155	SERESTO SMALL DOG	036007,129099	A 68 year old female in good condition with no known concomitant medical conditions, was secondarily exposed to a Seresto Small Dog collar to her hand while petting her dog. Immediately after exposure she experienced a strange taste in her mouth. About five weeks later she experienced joint pain.
027771 - 00008	2/16/2015	RICHMOND, VA	011556-00155	SERESTO DOG (UNSPECIFIED)	036007,129099	A 48 year old woman, in good condition, with an allergy to sodium tetraborate, was exposed daily to an unspecified amount of Seresto Dog collars after touching multiple dogs that had the product applied. The next day, she experienced erythema, pruritus, urticaria, blepharitis and lip edema. She took diphenhydramine orally. The clinical signs would resolved and recur and she continued to be exposed to the Seresto collars on the dogs.
028036 - 00019	6/6/2015	VA	011556-00155	SERESTO LARGE DOG	036007,129099	A 60 year old man, with no known concomitant medical conditions, was exposed to a Seresto Large Dog collar after applying to his dog. Approximately 1 week post exposure, the man had a bad taste in his mouth. Approximately three months later, the collar was removed from the dog in the home and a Seresto Small Dog collar was placed on the dog. The man recovered without medical intervention.
028097 - 00005	6/10/2015	VALENCIA, PA	011556-00155	SERESTO LARGE DOG	036007,129099	An adult female, with no known concomitant medical conditions was exposed to a Seresto Large Dog collar after placing the collar around her dog's neck. After exposure she developed respiratory irritation. Three months later, the collar was removed from the dog and disposed of and the respiratory sign resolved.
028097 - 00006	1/1/2015	JULIAN, PA	011556-00155	SERESTO (UNSPECIFIED)	036007,129099	An adult male, with no known concomitant medical conditions, was exposed to a Seresto Dog Collar after it was applied to the dog. An unknown time post exposure, the human was nauseated. Three month after the onset of symptoms, the collar was removed from the dog and the human recovered.
028341 - 00006	9/1/2015		011556-00155	SERESTO LARGE DOG	036007,129099	A 44 year old female, in good condition, with no known concomitant medical conditions was exposed to three Seresto Large Dog collars when she applied them to her dogs, one of which sleeps in her bed. Approximately 4 days post exposure, she developed eyelid inflammation and a burning sensation of her lips. The signs continued intermittently and she applied vitamin E oil to the affected skin. Three months after application, the collar was removed from the dog who sleeps in her bed. The signs continued and no medical examination has been sought.
028341 - 00007	7/1/2015		011556-00155	SERESTO SMALL DOG	036007,129099	A 48 year old female in fair condition with seasonal pollen allergies placed a Seresto Small Dog collar on her dog. The owner removed the dog's collar to bathe it. She put the collar back on the dog and

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Incident Description
						approximately 15 minutes post collar exposure, the woman developed a burning feeling to her right thumb.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: March 6, 2012

SUBJECT: Flumethrin: Human Health Risk Assessment for the Section 3 Registration Action for Cat and Dog Collars

PC Code: 036007
Decision No.: 440305
Petition No.:
Risk Assessment Type: Single Chemical/Aggregate
TXR No.:
MRID No.: 48240139

DP Barcode: D392125
Registration No.:
Regulatory Action: Section 3 Registration
Case No.: None

CAS No.: 69770-45-2
40 CFR:

FROM: Charles Smith, Senior Environmental Scientist/Risk Assessor
Marquea King, Ph.D., Toxicologist
Risk Assessment Branch VI
Health Effects Division (7509P)

THROUGH: Felecia Fort, Chief
Risk Assessment Branch VI
Health Effects Division

and

P.V. Shah, Ph.D.
Margarita Collantes
Risk Assessment Review Committee
Health Effects Division

TO: BeWanda Alexander/Richard Gebken, Risk Management Team 10
Insecticide Branch
Registration Division (7505P)
Risk Management Division

ED_005739A_00099209-00001

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. Bayer Healthcare LLC has requested registration of the new active ingredient (ai) flumethrin for use in cat and dog collars. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed pet collar uses of flumethrin.

HED has evaluated the toxicity and exposure databases for the new active ingredient, flumethrin, and has conducted a human health risk assessment in support of the proposed uses. Based on this assessment, HED has determined that there are no potential risk estimates of concern for the proposed uses of flumethrin. HED recommends that the requested uses be granted.

A summary of the findings and an assessment of human health risk resulting from the proposed uses for flumethrin are provided in this document. The HED team members contributing to this risk assessment include Marquea King (hazard evaluation) and Charles Smith (occupational/residential and risk assessment).

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1.0 Executive Summary

Bayer Healthcare LLC has requested registration of the new active ingredient (ai) flumethrin for use in cat and dog collars. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed pet collar uses of flumethrin. This document contains the human health exposure and risk assessment for the requested uses.

Use Profile: Flumethrin (*RS*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-(*EZ*)-3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate is a synthetic pyrethroid insecticide. Flumethrin is being proposed for use in cat and dog collars that also contain imidacloprid. There are two different sizes of collar being proposed both of which contain 4.5% flumethrin and 10% imidacloprid. The small collar weighs 12.5 grams and is intended for use on cats and small dogs up to 8 kg in weight. The large collar weighs 45 grams and is intended for use on dogs over 8 kg in weight.

Hazard Assessment: Pyrethroids have historically been classified into two groups, Type I and Type II, based upon chemical structure and neurotoxicological effect. Flumethrin is a Type II synthetic pyrethroid, which typically produce a distinct poisoning syndrome which is characterized by choreoathetosis (sinuous writhing of the whole body) and excessive salivation also known as CS syndrome. The data base of experimental toxicology studies available for flumethrin provides a robust characterization of the hazard. There are no outstanding studies according to Part 158 data requirements for a non-food use pesticide registration. In addition, numerous studies from the scientific literature that describe the pharmacodynamic and pharmacokinetic profile of the pyrethroids in general have been considered in this assessment.

Flumethrin has been evaluated for a variety of toxic effects in experimental toxicity studies. Neurobehavioral changes characteristic of Type II pyrethroids (i.e., pawing, burrowing, salivation, and coarse tremors leading to choreoathetosis (CS-syndrome)) were observed at high doses in experimental toxicology studies with flumethrin. Specifically, profuse salivation has been observed in a variety of guideline flumethrin toxicological studies. Although salivation was observed in nearly all experimental studies in all species and durations, the decreased motor activity observed in the acute neurotoxicity (ACN) study was selected as the endpoint for risk assessment. Decreased motor activity was the most sensitive endpoint identified for flumethrin and is protective of the salivation seen throughout the database. Additional effects seen in one or more studies included hind-limb swelling, digit eating, and staining. Flumethrin also produced decreased body weights, body weight gains, and food consumption in repeat dosing studies at similar doses that produced decreased motor activity in the ACN.

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. Following a single oral gavage dose, flumethrin is absorbed quickly in rats displaying decreased motor activity and increased salivation, neurotoxicity is observed within 5 hours, and rats recover within 24 hours without any persisting neurotoxic effects. This is generally consistent with the toxicity profiles for all the pyrethroids which are very similar and marked by rapid absorption, metabolism, and time-to-peak effect.

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The NOAELs and LOAELs established from flumethrin single dose and repeat dosing studies show that repeat exposures do not result in lower NOAELs. Thus for purposes of endpoint selection and exposure assessment, only single day risk assessments need to be conducted.

Evidence of increased qualitative or quantitative susceptibility of the offspring was not observed in any of the available animal testing guideline toxicity studies. However, the Agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age based on the following: 1) age-dependent pharmacokinetics, supported by rat Physiologically Based Pharmacokinetic (PBPK) model predictions of a 3-fold increase of pyrethroid concentration in juvenile brain compared to adults; 2) *in vitro* pharmacodynamic (PD) data and *in vivo* data indicating similar responses between adult and juvenile rats at low doses; and 3) data indicating that the rat is a conservative model compared to the human based on species-specific pharmacodynamics of homologous sodium channel isoforms.

Quantification of dermal risks was performed using a 90-day dermal rat study with a NOAEL of 10 mg/kg/day based on loss of hair; decreased body weight and body weight gain (males); decreased erythrocytes; high stepping gait; and increased absolute spleen weight (LOAEL = 30 mg/kg/day). Quantification of incidental oral ingestion risks was performed using the rat acute neurotoxicity study with a NOAEL of 0.5 mg/kg/day based on decreased motor/locomotor activity; increased staining of the mouth, perianal, and nose; increased lacrimation; and increased salivation (LOAEL = 1 mg/kg/day). Quantification of inhalation risks is not required as handler and post-application inhalation exposure is expected to be negligible from the proposed flumethrin pet collars.

There were no treatment related increases in tumor incidences when compared to controls in both the rat chronic toxicity/carcinogenicity study and the carcinogenicity mouse study. In accordance with the Agency's 2005 Cancer Guidelines, there was no evidence of carcinogenicity in either species and this chemical is classified as "Not likely to be carcinogenic to humans".

Food Residue Profile: There are no proposed or currently registered food uses for flumethrin.

Dietary Exposure and Risk: A dietary (food + drinking water) exposure assessment is not required, since there are no proposed or currently registered food uses for flumethrin and drinking water exposure is not expected from the proposed uses.

Residential Exposure: Residential handler exposures to flumethrin pet collars may occur via the dermal route. The durations of handler exposure relevant to the proposed use pattern are short-term because the proposed pet collar has an efficacious life of 8 months (i.e., a collar would only be applied once every 8 months). However, the available toxicological data supports the conclusion that neurotoxicity from flumethrin and pyrethroids in general is associated with acute, peak exposures. As such, only single day dermal risks were assessed. No risks of concern for residential handler exposure were identified in this assessment.

Residential post-application exposures to flumethrin can also occur after collars are placed on a cat or dog via dermal and oral exposure routes. The durations of exposure relevant to the proposed use pattern are short-term, intermediate term, and chronic as flumethrin pet collars

could potentially be used year round. However, the available toxicological data supports the conclusion that neurotoxicity from flumethrin and pyrethroids in general is associated with acute, peak exposures. As such, only single day dermal risks were assessed. Dermal post-application risks were assessed for adults and children 1 < 2 years old while oral (hand-to-mouth) post-application risks were assessed for children 1 < 2 years old. No risks of concern for residential post-application exposure were identified in this assessment.

Aggregate Risk: There are currently no registered food uses for flumethrin and drinking water exposure is not expected from the proposed pet collar uses of flumethrin; therefore, a quantitative aggregate risk assessment is not required at this time.

Occupational Exposure/Risk: For the proposed flumethrin pet collar uses, occupational handler exposures are expected to be less or at worst case equal to the residential handler exposures as this is traditionally considered a consumer product as opposed to one applied by veterinarians or professional groomers. As a result, no quantitative occupational handler exposure and risk assessment has been performed. The residential handler exposure and risk assessment is considered protective for any potential occupational handler exposures and risks.

For the proposed flumethrin pet collar uses, occupational post-application exposure could potentially occur, however; these types of exposures are not expected to be greater than residential post-application exposures (i.e., minimal and infrequent contact by a professional animal care worker is expected to occur after a collar is applied). As a result, no quantitative occupational post-application exposure and risk assessment has been performed. The residential post-application exposure and risk assessment is considered protective for any potential occupational post-application exposures and risks.

Review of Human Research: This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies (listed in Appendix B) have been determined to require a review of their ethical conduct and all of the studies utilized in this assessment have received the appropriate review.

2.0 HED Recommendations

HED has evaluated the toxicity and exposure databases for the active ingredient, flumethrin, and has conducted a human health risk assessment in support of the proposed uses. Based on this assessment, HED has determined that there are no potential risk estimates of concern for the proposed uses of flumethrin. HED recommends that the requested uses be granted.

2.1 Data Deficiencies

The following data would allow HED to refine the flumethrin risk assessment:

EXPOSURE

A flumethrin pet transferable residue study (i.e., a petting study) would allow HED to refine the residential post-application exposure and risk assessment. This study has become the standard study for use in assessing the amount of pesticide residue that is available for transfer from pets. HED encourages the registrant to submit a protocol to the Agency for review before initiation of the study.

The following data would allow HED to refine the flumethrin relative potency factor in the pyrethroid cumulative risk assessment:

TOXICOLOGY

The existing toxicology database for assessment of flumethrin as a single chemical is complete with respect to the guideline requirements for a non-food use pesticide. However, unlike most of the other pyrethroids, a specially designed functional observational battery (FOB) study is not available for use in estimating relative potency for purposes of cumulative risk assessment. Such FOB data are available for 17 other pyrethroids and these data provide the basis for high confident relative potency factors in the pyrethroid cumulative (USEPA, 2011a). As such, the data used in the estimated RPF for flumethrin does not represent such a uniform measure of potency and introduces some uncertainty in the cumulative risk assessment. In lieu of this data, the Agency used the flumethrin acute neurotoxicity study to estimate an RPF for flumethrin (see Appendix D for more details). Although the Agency believes the estimated RPF does not underestimate the contribution of flumethrin to the pyrethroid cumulative risk assessment, a flumethrin FOB study would allow the Agency to develop an RPF using a uniform measure of relative potency and thus reduce the uncertainty introduced by the lack of such data. HED encourages the registrant to develop such special FOB data. In the event that the registrant elects to develop these data, HED further encourages the submission of a protocol to the Agency for review before initiation of the study.

2.2 Tolerance Considerations

There are no established or proposed tolerances for flumethrin in or on any food or feed crops.

2.3 Label Recommendations

2.3.1 Recommendations from Residential Assessment

No label revisions are needed for residential exposure purposes and no recommendations are being made by HED.

2.3.2 Recommendations from Occupational Assessment

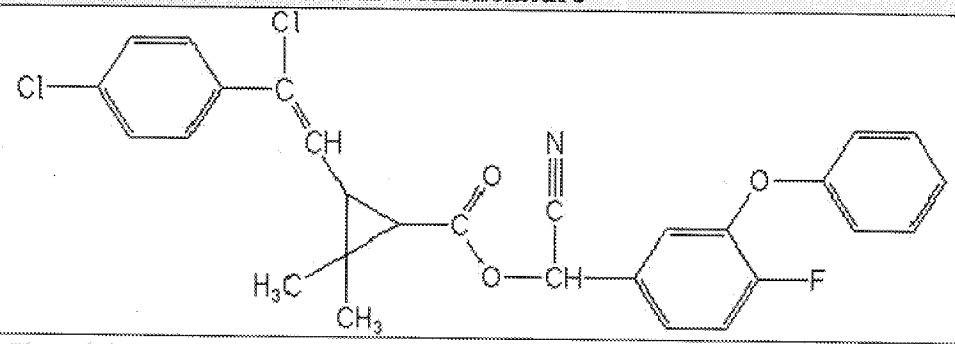
No label revisions are needed for occupational exposure purposes and no recommendations are being made by HED.

3.0 Ingredient Profile

Flumethrin is a new synthetic pyrethroid insecticide.

3.1 Structure and Nomenclature

Table 3.1: Flumethrin Nomenclature

Chemical Structure	
Common Name	Flumethrin
IUPAC name	(*RS*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-(*EZ*)-3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate
CAS Name	cyano(4-fluoro-3-phenoxyphenyl)methyl 3-[2-chloro-2-(4-chlorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate
CAS Registry Number	69770-45-2
Chemical Class	Synthetic pyrethroid

3.2 Physical/Chemical Characteristics

Table 3.2: Flumethrin Physical and Chemical Properties	
Parameter	Value
Molecular Weight	510.4 g/mol.
Boiling Point	>250°C
Water solubility (20°C)	9.7×10^{-5} mg/l
Solvent solubility (20°C)	No Data
Vapor pressure (25°C)	3.9×10^{-9} mm Hg
Henry's Law Constant (25°C)	4.2×10^{-8} atm-m^3/mol
Octanol/water partition coefficient	log Kow = 7.65

3.3 Summary of Existing/Proposed Uses

Flumethrin is a new active ingredient being proposed for use as an ectoparasiticide for the control of ticks, lice, and mites (pet collars) for use in cat and dog collars that also contain imidacloprid. There are two different sizes of collar being proposed both of which contain 4.5% flumethrin and 10% imidacloprid. The small collar weighs 12.5 grams and is intended for use on cats and small dogs up to 8 kg in weight. The large collar weighs 45 grams and is intended for use on dogs over 8 kg in weight. The collars have an efficacious life of 8 months. There are restrictions on the label preventing use of collars on kittens under 7 weeks of age or puppies under 10 weeks of age.

3.4 Anticipated Exposure Pathways

The Registration Division has requested an assessment of human health risk to support the proposed new uses of flumethrin in cat and dog collars. Humans are not expected to be exposed to flumethrin in their diet as the proposed pet collar uses of flumethrin are considered to be non-food uses. Drinking water exposure is also not expected based on the proposed pet collar uses of flumethrin. The proposed uses will potentially result in residential handler and post-application exposures. Additionally, there is a potential for occupational handler and post-application exposure to pet care professionals.

These are the first registrations proposed for flumethrin in the United States; therefore, this is the first risk assessment prepared by the Agency to address potential risks associated with the use of this new active ingredient.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption,

and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Flumethrin is a member of the pyrethroid class of chemicals. Pyrethroids have historically been classified into two groups, Type I and Type II, based upon chemical structure and neurotoxicological effect. Type I pyrethroids, which lack an alpha-cyano moiety, induce in rats a syndrome consisting of aggressive sparring, altered sensitivity to external stimuli, and fine tremor progressing to whole-body tremor and prostration (T-syndrome). Type II pyrethroids, which contain an alpha-cyano moiety, in rats produce a syndrome that includes pawing, burrowing, salivation, and coarse tremors leading to choreoathetosis (CS-syndrome) (Verschoyle and Aldridge 1980; Lawrence and Casida 1982). Flumethrin is a Type II synthetic pyrethroid. The adverse outcome pathway (AOP) shared by pyrethroids involves the ability to interact with voltage-gated sodium channels (VGSCs) in the central and peripheral nervous system, leading to changes in neuron firing, and ultimately neurotoxicity (see Figure 1).

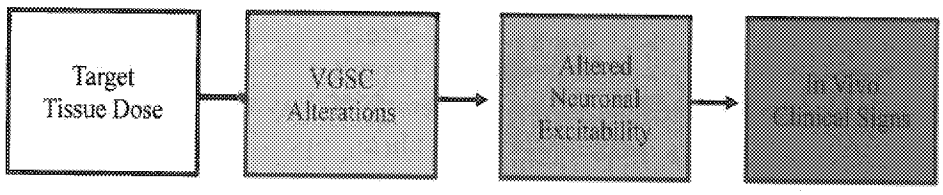


Figure 1. Adverse outcome pathway for pyrethroids

4.1 Toxicology Studies Available for Analysis

The data base of experimental toxicology studies available for flumethrin provides a robust characterization of the hazard potential for children 6 years old and older and for adults. There are no outstanding studies according to Part 158 data requirements for a non-food use pesticide registration. However, there are on-going efforts to develop data to inform the potential sensitivity of infants and younger children to pyrethroids as a class which is discussed further in Section 4.4. Despite these scientific efforts, HED is confident that it has chosen points of departure and uncertainty factors in this risk assessment which are health protective and have a strong scientific foundation.

The data from the following studies were used to evaluate the hazard potential of flumethrin:

-Developmental Rat Studies
-Developmental Rabbit Studies
-Reproduction Rat Study
-Chronic/Cancer Mouse Study
-Chronic/Cancer Rat Study
-28 Day Mouse Study
-90- Day Rat and Mouse Study
-Acute Neurotoxicity (ACN) Rat Study
-Subchronic Neurotoxicity (SCN) Rat Study
-Developmental Neurotoxicity (DNT) Rat Study
-14-day, 28-day, and 90-day Dermal Rat Study
-28-day Inhalation Rat Study
-Genotoxicity Studies
-Immunotoxicity Study
-Metabolism and Pharmacokinetics

The studies available for consideration of flumethrin toxicity provide a comprehensive database. In addition, numerous studies from the scientific literature conducted over several decades describe the pharmacodynamic and pharmacokinetic profile of the pyrethroids in general; this scientific literature has been recently reviewed by several groups (Wolansky and Harrill 2008; Weiner et. al. 2009). Although none of this literature provides any specific data on flumethrin, because of the shared toxicological properties of the members of this class of pesticides, these studies are informative in the hazard characterization of flumethrin.

4.2 Flumethrin Toxicological Profile

Flumethrin has been evaluated for a variety of toxic effects in guideline experimental toxicity studies. Neurobehavioral changes characteristic of Type II pyrethroids (e.g., pawing, burrowing, salivation, and coarse tremors leading to choreoathetosis (CS-syndrome)) were observed at high doses in experimental toxicology studies with flumethrin. Specifically, profuse salivation has been observed in the following guideline flumethrin toxicological studies: developmental rat toxicity studies; the developmental neurotoxicity study; sub-chronic rat toxicity studies; acute and sub-chronic rat neurotoxicity studies; 90-, 21-, and 14-day dermal rat toxicity studies; and chronic mouse oral toxicity studies. Although salivation was observed in nearly all experimental studies in all species and durations, the decreased motor activity observed in the acute neurotoxicity (ACN) study was selected as the endpoint for risk assessment. Decreased motor activity was the most sensitive endpoint identified for flumethrin and is protective of the salivation seen throughout the database. Additional effects seen in one or more studies included hind-limb swelling, digit eating, and staining. Flumethrin also produced decreased body weights, body weight gains, and food consumption in repeat dosing studies at similar doses that produced decreased motor activity in the ACN. Regarding gender, males were found to be more sensitive throughout the database (i.e., males were found to have lower NOAELs versus females in the mouse carcinogenicity, rat subchronic, dermal, reproductive, ACN, and SCN studies).

The potential reproductive toxicity of flumethrin was examined in a multi-generation reproduction study in the rat. Parental toxicity was expressed as reductions in pituitary weights (F1 generation) for males at the low dose and reduction in liver weights in females (F0 and F1 generations) at the mid-dose. Offspring toxicity was expressed by decreased body weight, decreased rearing indexes, and deaths at post natal days 0-4, all occurring at the high dose. Developmental studies in both rats and rabbits had NOAELs based on increased salivation, decreased body weight gains and food consumption. Maternal effects showed slight increases in abortions and increased swelling of the limbs at the highest dose tested.

The pharmacokinetics of flumethrin is similar to other pyrethroids, i.e., rapid absorption and clearance. Following a single oral dose, flumethrin was excreted mainly via the feces (68%) within 24 hours. In radiolabeled flumethrin studies, absorbed radioactivity calculated as the sum of urine, bile and body tissues accounts for 75% of the given dose in bile duct-cannulated rats, indicating a high level of absorption following an oral dose. The rapid absorption was also observed in an exploratory PK study where the maximum plasma levels of flumethrin were found at 2 and 4 hours after administration for each dose level.
The acute toxicity profile of flumethrin consists of mild toxicity via the oral, dermal, and inhalation routes of exposure (Category II). The eye irritation study was indicates that the technical is an amorphous glass-like solid that does not exist as a fine powder at room temperature and so cannot be tested by this exposure route. A waiver was granted for the eye irritation study with assignment to toxicity category IV by this exposure route. Flumethrin was assigned to Category IV as a skin irritant. The dermal sensitizer study was deemed unacceptable but can be upgraded to acceptable with adequate reporting classification of the test material.

4.2.1 Critical Duration of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. Following a single oral gavage dose, flumethrin is absorbed quickly in rats displaying decreased motor activity and increased salivation, neurotoxicity is observed within 5 hours, and rats recover within 24 hours without any persisting neurotoxic effects. This is generally consistent with the toxicity profiles for all the pyrethroids which are very similar and marked by rapid absorption, metabolism, and time-to-peak effect. The NOAELs and LOAELs for both motor activity changes and decreases in body weight established from results of experimental toxicity studies with flumethrin are remarkably consistent across durations of exposure ranging from a single dose up to 2-years of dosing (see Table 4.3).

Table 4.3: Experimental Toxicology Studies with Similar Results			
Study	Duration	Study findings (mg/kg/day)	
Acute Neurotoxicity	Acute, single exposure	NOAEL = 0.5	LOAEL = 1.0
Developmental neurotoxicity	86 days	NOAEL = 1.0	LOAEL = 2.0
Sub-chronic mouse	90 day	NOAEL = 0.9	LOAEL = 1.4
Sub-chronic rat	90 day	NOAEL = 0.7	LOAEL = 2.9
Sub-chronic neurotoxicity	90 day	NOAEL = 1.0	LOAEL = 2.6
Reproductive toxicity	120 days	NOAEL = 0.2	LOAEL = 2.4
Chronic-carcinogenicity rat	2-year	NOAEL = 0.7	LOAEL = 2.0
Carcinogenicity mouse	2-year	NOAEL = 0.4	LOAEL = 2.0

Looking at the NOAELs and LOAELs established from flumethrin single dose and repeat dosing studies it is apparent that repeat exposures do not result in lower NOAELs. This is consistent with the general kinetic profile for the pyrethroids. The LOAEL from the ACN (1.0 mg/kg) is the same as chronic 2-year cancer study (LOAEL 2.0 mg/kg/day). Therefore, the endpoint from the acute study is protective of the endpoints from the repeat dosing studies. Thus for purposes of endpoint selection and exposure assessment, only single day risk assessments need to be conducted.

4.3 Pyrethroid Pharmacokinetic and Pharmacodynamic Profile

The extensive body of scientific literature on the pyrethroids provides a unique insight into the contributions of pharmacokinetics (PK) and pharmacodynamics (PD) to the general toxicity profile of this class of chemicals. This information also provides valuable insight into the potential age-related differences in toxicity for the pyrethroids. The following sections discuss the specific issues related to pyrethroid pharmacokinetics, pyrethroid pharmacodynamics, and age-related differences in pyrethroid toxicity.

4.3.1 Pharmacokinetics

Pharmacokinetics can be defined as what the body does to the chemical; in this case, how pyrethroids are distributed and eliminated following exposure. Specific to pyrethroids, PK refers to the process(es) which determine the concentration of the pyrethroids reaching sodium channels. The underlying pharmacokinetics of pyrethroids is an important determinant of their toxicity because the concentration of pyrethroid at the sodium channel relates to the extent of toxicity; greater pyrethroid concentration translates as increased neurotoxicity. Two physiological processes that significantly contribute to the PK include metabolism and partitioning. Carboxylesterases and P450 enzymes are the two major enzyme families responsible for metabolism of pyrethroids. It is the ontogeny of these enzymes that accounts for the age-related sensitivity observed after pyrethroid exposures. With respect to the partitioning of pyrethroids within the body, pyrethroids are highly lipophilic and preferentially deposit in fatty tissue such as adipose compared to leaner tissues such as muscle. Pyrethroid residues in fatty tissue are not available to interact with the VGSCs in vital tissues and therefore do not contribute to overall toxicity.

Physiologically-based pharmacokinetic (PBPK) models, designed to predict pyrethroid concentration in tissues following *in vivo* exposure, have recently been developed by the Agency. The Agency has determined that the important PK properties relevant for the metabolism and distribution of pyrethroids in the body are sufficiently similar for members of this class such that using a 'generic' or family model structure for this class is scientifically appropriate. In other words, due to the similarities in the PK profiles of pyrethroids, a single model structure is able to predict the tissue dose based on the pharmacokinetics of every member of the class. The family modeling approach was presented to and supported by the FIFRA SAP (USEPA 2007).

In 2011 the Agency conducted an analysis of the toxicokinetic profile of pyrethroids as a class. Several studies in this analysis indicate that there are age-dependent pharmacokinetic differences for the pyrethroids (i.e., there are differences in the ability of adults and juveniles to metabolize pyrethroids). The enzymes which metabolize and detoxify the pyrethroids are present in rats and humans at birth (Koukouritaki et. al. 2004; Yang et. al. 2009). As a result, both juveniles and adults are able to tolerate low doses of pyrethroids when the internal dose, or the amount of pyrethroid at the sodium channel, is low. However, the activity of these enzymes increases with age, conveying in adults a greater capacity to detoxify pyrethroids compared to juveniles (Anand et. al. 2006; de Zwart et. al. 2008; Yang et. al. 2009). For example, the rate of *in vitro* metabolism of deltamethrin by plasma carboxyesterases, hepatic carboxyesterases, and hepatic microsomes are at least 6 times higher for PND 90 rats compared to PND 10 rats (Anand et. al. 2006). As a consequence, higher internal doses (i.e., those associated with high doses in experimental toxicology studies) overwhelm the clearance mechanisms in juveniles but because adults have greater enzyme activity, they are able to tolerate higher doses prior to the onset of toxicity. As a matter of perspective, the anticipated exposures from typical dietary or residential activities are not expected to overwhelm the premature metabolic systems in juveniles.

Predictive PBPK models have recently been developed to describe the PK of a few pyrethroids (Mirfazaelian et. al. 2006; Godin et. al. 2010). Among these is an age-dependent model developed by the Agency which is capable of predicting the concentration of deltamethrin in the brains of rats at multiple ages (Tornero-Velez et. al. 2010). The brain is considered the primary target organ for pyrethroids and increased pyrethroid concentrations are correlated with increasing systemic toxicity. This model predicts that, compared to adult rats (i.e., 90-days old), equivalent brain concentrations of deltamethrin would be achieved with a 3.8X fold lower oral dose in 10-day old rats and 2.5X lower dose in 21-day old rats (Tornero-Velez et. al. 2010). For example, a 1 mg/kg dose in the adult is equivalent to a 0.26 mg/kg dose (≈1 mg/kg÷3.8mg/kg) in the 10-day old rats and to a 0.4 mg/kg (≈1 mg/kg÷2.5mg/kg) dose in a 21-day old rat. The difference between a 3.8- and a 2.5-fold dose is within background variability of the model. As a result, the Agency concludes that juvenile rats are 3x more sensitive than adults with respect to pyrethroid pharmacokinetics.

4.3.2 Pharmacodynamics

Pharmacodynamics (PD) can be defined as the changes that chemicals cause to the body, in this case, how pyrethroids interact with the sodium channels. Substantial evidence from *in vitro* and *in vivo* studies support the AOP illustrated in Figure 1 above as well as disruption of sodium

channels by pyrethroids as an early key event in this AOP (Lund and Narahashi 1982; Salgado et. al. 1989; Song and Narahashi 1996; Tabarean and Narahashi 1998; Soderlund et. al. 2002 (review)). As a new active ingredient, there are no recent studies for flumethrin which provide information on how flumethrin interacts with the sodium channels. However, there are several recent studies which provide information on a variety of other pyrethroids. Choi and Soderlund (2006) examined interactions of several pyrethroids with mammalian VGSCs expressed in *Xenopus* oocytes. With respect to altered neuronal excitability, Type I pyrethroids cause slight prolongations of the sodium current tails (e.g. ~20 ms), often resulting in long trains of action potentials. In contrast, Type II pyrethroids significantly prolong sodium current tails (e.g. 200ms to minutes) typically resulting in increased resting membrane potential and ultimately causing depolarization dependent action potential block. Cao et. al. (2011a) measured Na influx in primary cultures of mammalian (mouse) neurons and demonstrated that pyrethroids caused increases in Na influx in this model; this confirms the ability of pyrethroids to interact with VGSC in intact mammalian neurons. An additional study by Cao et. al. (2011b) demonstrated that the interaction of pyrethroids with VGSC caused changes in neuronal excitability that resulted in calcium influx into intact mouse neurons.

HED would prefer to use an early key event in the AOP for pyrethroids in selection of points of departure. However, i*n vivo* techniques used to detect VGSC alteration and altered neuronal excitability are not practical for use in risk assessment at this time and approaches for extrapolating *in vitro* findings to *in vivo* measures are not yet developed. As such, the Agency is focusing its efforts for all pyrethroids in hazard characterization and identification on the apical endpoint (i.e., changes in neurobehavior in laboratory animals). Neurotoxicity resulting from pyrethroids are generally characterized by tremors, hyper- or hypothermia, heightened response to stimuli, salivation, tremors and convulsions (Nemec 2006; Wolansky and Harrill 2008; Breckenridge et. al. 2009).

In contrast to the age-related PK differences identified in the 2011 analysis, PD contributions to pyrethroid toxicity are not age-dependent even though there are several variations of sodium channels, called isoforms, which are differentially expressed by tissue and age. Due to the nature of the interaction of pyrethroids with sodium channels, it is difficult to obtain dynamic information *in vivo*. To date, a readily useable biomarker of *in vivo* pyrethroid interaction with sodium channels has not been identified, making it impractical to determine the isoform combinations that are present and being acted upon by pyrethroids. Therefore, much of the information available to the Agency to characterize the PD relationship between pyrethroids and sodium channels has been derived from *in vitro* studies using frog oocytes or nervous cells artificially grown in media. While these *in vitro* techniques do not provide direct quantitative measure of *in vivo* pyrethroid activity, they consistently and qualitatively demonstrate that channel isoforms expressed in juveniles are not more sensitive to pyrethroid perturbation compared to isoforms expressed in adults and that, pharmacodynamically, the rat is a conservative model for humans. For example, Meacham et al. (2008), compared the sensitivity of an adult isoform and a juvenile isoform expressed in frog oocytes to deltamethrin. The isoforms had comparable responses at environmentally relevant concentrations (<500 nM) of deltamethrin, suggesting a lack of PD difference between juveniles and adults at low exposure levels. In addition, in a direct comparison of a homologous rat and human VGSC isoform, NaV1.3, Tan and Soderlund, (2009) found the rat isoform was 4-fold more sensitive than the

equivalent human sodium channel to the pyrethroid tefluthrin (Tan and Soderlund 2009), suggesting the rat is a highly sensitive model and extrapolations from the rat would be protective of human health. The occurrence and ontogeny of voltage-gated sodium channels in humans is not well characterized compared to the rat. However, based on the comparable function and distribution of sodium channels between the species, the rat is an appropriate surrogate for the evaluation of human PD (Goldin et. al. 2000; Goldin 2002). As a result, the Agency concludes that juvenile rats are not more sensitive than adults with respect to pyrethroid pharmacodynamics.

4.4 Consideration of Toxicity to Children

Food Quality Protection Act (FQPA) considerations do not apply to flumethrin for the proposed (non-food) use patterns described in this risk assessment. However, since flumethrin is a pyrethroid and exposure to children under <6 years old is expected, flumethrin must be considered in the greater context of the pyrethroids as a class. The Agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age based on the increased quantitative susceptibility seen in the scientific literature related to pyrethroid pharmacokinetics. This is consistent with the Agency's 2011 analysis and is supported by rat PBPK model predictions of a 3-fold increase of deltamethrin concentrations in the juvenile brain compared to adults (see Section 4.3.1). The PK of pyrethroids as a group is sufficiently similar that significant deviations from the 3-fold increase of deltamethrin concentrations are not expected for other pyrethroids. As noted in Section 4.3.2, juveniles are not more sensitive than adults with respect to pyrethroid pharmacodynamics and thus no uncertainty factor is needed for PD considerations.

4.4.1 Completeness of the Toxicology Database

There are no residual uncertainties with regard to the flumethrin toxicological database. Flumethrin has all of the required toxicity studies to assess the current non-food use.

4.4.2 Evidence of Neurotoxicity

There are no residual uncertainties with regard to evidence of neurotoxicity for flumethrin. Flumethrin, like other pyrethroids, causes neurotoxicity from interaction with sodium channels leading to clinical signs of neurotoxicity. Neurotoxicity was consistently observed throughout the database in a dose-dependent manner in most all of the studies conducted. The mode of action is fully characterized and indications of neurotoxicity included salivation typical of Type II pyrethroid compounds.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Based on the flumethrin-specific data and the extensive body of peer-reviewed literature on pyrethroids available, the Agency reached a number of conclusions including the following:

- The Agency has no residual uncertainties regarding age related sensitivities for women of child bearing age as well as for all adult populations and children > 6 years of age,

based on the absence of pre-natal sensitivity observed in 76 guideline studies for 24 pyrethroids, the scientific literature, and the flumethrin guideline toxicological studies.

- Although the flumethrin toxicological database was not considered in the 2011 analysis, the flumethrin developmental, reproductive, and DNT toxicity studies are consistent with other members of the pyrethroid class in that no evidence of increased quantitative or qualitative susceptibility was observed in these studies.
- No evidence of increased quantitative or qualitative susceptibility was seen in the pyrethroid scientific literature related to pharmacodynamics.
- The Agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age based on the increased quantitative susceptibility seen in the scientific literature related to pyrethroid pharmacokinetics.

The Agency is aware that additional *in vitro* and *in vivo* studies are currently being conducted that could potentially inform a number of issues related to pyrethroid toxicity as a class. In 2010, the Agency requested proposals for study protocols which could identify and quantify potential juvenile sensitivity and received a single, coordinated response from the Pyrethrin and Pyrethroids Working Group (PPTWG), a conglomerate of pyrethroid registrants. The PPTWG protocol was reviewed during a July 2010 FIFRA SAP meeting[1]. Based on comments from the SAP, the initial study proposal was refined. At present time, pesticide registrants and product formulators have come together as Council for the Advancement of Pyrethroid Human Risk Assessment (CAPHRA) and plan on doing the following: 1) conducting *in vitro* studies demonstrating the interaction of pyrethroids exogenously expressed rat and human VGSCs in *Xenopus* oocytes; 2) conducting *in vitro* studies demonstrating interaction of pyrethroids in rat neurolemma cells; 3) developing rat and human PBPK models, including additional pharmacokinetic data; and 4) conducting *in vivo* behavioral testing using auditory startle testing in rats. As these data becomes available, the Agency will determine whether re-evaluation of the age-related sensitivity of pyrethroids is appropriate.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to residential exposure. The residential exposure assessment is based on conservative, health-protective assumptions that ensure that exposures to the proposed flumethrin pet collars are not underestimated.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

The details for selecting toxicity endpoints and points of departure (PODs) are presented in Appendix A2. Based on the proposed use pattern for flumethrin in pet collars, the expected exposure profile will be for dermal and incidental oral exposures. Therefore, acute dietary and inhalation endpoints were not established.

Acute Dietary: The current proposed use is for a non-food pet collar use. Acute dietary PODs have not been established for this risk assessment.

[1] http://www.epa.gov/scipoly/sap/meetings/2010/072310meeting.html

Short-term Dermal: Quantification of dermal risks was performed using a 90-day dermal rat study with a NOAEL of 10 mg/kg/day based on loss of hair; decreased body weight and body weight gain (males); decreased erythrocytes; high stepping gait; and increased absolute spleen weight (LOAEL = 30 mg/kg/day).

Short-term Incidental Oral: Quantification of incidental oral ingestion risks was performed using the rat acute neurotoxicity study with a NOAEL of 0.5 mg/kg/day based on decreased motor/locomotor activity; increased staining of the mouth, perianal, and nose; increased lacrimation; and increased salivation (LOAEL = 1 mg/kg/day).

Short-term Inhalation: Quantification of inhalation risks is not required as handler and post-application inhalation exposure is expected to be negligible from the proposed flumethrin pet collars.

4.5.2 Recommendation for Combining Routes of Exposure for Risk Assessment

HED combines risk values resulting from separate exposure pathways when it is likely they can occur simultaneously based on the use pattern, the behavior associated with the exposed population, and the hazard associated with the points of departure. For flumethrin, the points of departure are based on different effects and thus it is not appropriate to combine the dermal and oral exposure scenarios.

4.5.3 Cancer Classification and Risk Assessment Recommendations

In neither a rat chronic toxicity/carcinogenicity study nor a carcinogenicity mouse study, both conducted with adequate doses, were there treatment related increases in tumor incidences when compared to controls. In accordance with the Agency's 2005 Cancer Guidelines, there was no evidence of carcinogenicity in either species and this chemical is classified as "Not likely to be carcinogenic to humans".

4.5.4 Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5: Summary of Toxicological Doses and Endpoints for Flumethrin

Exposure Scenario	Dose Used in Risk Assessment, UF	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term (1-30 days) Incidental Oral	NOAEL= 0.5 mg/kg/day	UF_A = 10x UF_H = 10x, UF_{QS} = 3x	Residential LOC for individuals < 6 years old = 300	Acute Neurotoxicity Study LOAEL= 1 mg/kg/day in males based on ↓motor/locomotor activity, ↑staining of mouth, perianal, nose, ↑lacrimation, salivation at ↑doses
Short-Term (1-30 days) Dermal	NOAEL = 10 mg/kg/day	UF_A = 10x UF_H = 10x UF_{QS} = 3x	Residential LOC for individuals < 6 years old = 300 Residential LOC for individuals > 6 years old = 100 Occupational LOC = 100	90-day Dermal Study LOAEL=30 mg/kg/day Based on loss of hair; ↓BW and ↓BWG (M), ↓erythrocytes, high stepping gait, ↓ABS spleen wt,
Short-Term (1-30 days) Inhalation	N/A	N/A	N/A	N/A
Cancer (oral, dermal, inhalation)	**Classification:** "Not likely" to be carcinogenic in humans			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{QS} = to account for the quantitative susceptibility to children <6 years of age. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

5.0 Dietary Exposure and Risk Assessment

5.1 Food Residue Profile

There are no proposed or currently registered food uses for flumethrin.

5.2 Water Residue Profile

Drinking water exposure is not expected based on the proposed pet collar uses of flumethrin.

5.3 Dietary Risk Assessment

A dietary (food + drinking water) exposure assessment is not required, since there are no proposed or currently registered food uses for flumethrin and drinking water exposure is not expected from the proposed uses.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Residential handler exposures to the proposed flumethrin pet collars may occur via the dermal route while the collars are placed on a cat or dog. Additionally, residential post-application exposures to flumethrin can also occur after collars are placed on a cat or dog via dermal and oral exposure routes. In assessing these exposures, the *Health Effects Division's 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment: Treated Pets* was used.

Some of the data included in the Treated Pet SOP are proprietary and thus are subject to the data protection provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

6.1 Residential Handler Exposure and Risk

Residential handler exposures to the proposed flumethrin pet collars may occur via the dermal route while the collars are placed on a cat or dog. Residential handler inhalation exposure is expected to be negligible from flumethrin pet collars and thus a quantitative assessment was not performed. Based on the proposed flumethrin pet collar label, HED has assumed that the proposed pet collars are mainly directed towards homeowner use. As a result, a dermal residential handler exposure assessment was performed for homeowners applying the collar to a cat or dog. The durations of handler exposure relevant to the proposed use pattern are short-term because the proposed pet collar has an efficacious life of 8 months. However, the available toxicological data supports the conclusion that neurotoxicity from flumethrin and pyrethroids in general is associated with acute, peak exposures (i.e., every day is a new day). As such, only single day dermal risks were assessed. Dermal handler risks were assessed only for adults.

No chemical-specific unit exposure data were provided in support of this submission and there are currently no surrogate exposure data available for applying pet collars. As a result, HED used exposure data described in the 2012 Treated Pet SOP for spot-on applications (MRID 44433303) as a health protective surrogate to estimate handler exposures for applying collars. These unit exposures were based on residential handlers wearing short pants, short-sleeved shirt, and no gloves. In addition to this data, exposure algorithms (see Appendix C) and other standard assumptions (e.g., number of pets treated) were taken from the 2012 Treated Pet SOP.

HED's level of concern for adult residential handlers is equal to an MOE of 100. All residential handler dermal exposure scenarios do not exceed HED's level of concern (i.e., MOEs ≥ 100). Handler exposure and risks are summarized in Table 6.1.1.

Table 6.1.1: Residential Handler Exposure and Risk for Flumethrin

Scenario	Dermal Unit Exposure [a] (mg/lb ai)	Application Rate [b]		Amount Treated [c]	Dermal Dose [d] (mg/kg/day)	Dermal MOE [e]
Applying Pet Collars	120	Small collar (12.5 gram)	0.00124 lb ai/collar	2 pets	0.0037	2,700
		Large collar (45 gram)	0.00446 lb ai/collar		0.013	750

a. Data taken from 2012 Treated Pets SOP (MRID 44433303)
b. Small collar application rate: 12.5 gram collar x 4.5% flumethrin x 0.0022 lb/g = 0.00124 lb ai flumethrin per collar
Large collar application rate: 45 gram collar x 4.5% flumethrin x 0.0022 lb/g = 0.00446 lb ai flumethrin per collar
c. Data from the American Pet Products Manufacturers Association (APPA) 2011-2012 National Pet Owners Survey as presented in the 2012 Treated Pets SOP
d. Dermal Dose (mg/kg/day) = unit exposure (mg/lb ai) * application rate * amount treated/ body weight (80 kg).
e. Dermal MOE = NOAEL (10 mg/kg/day)/Dermal Dose

6.2 Residential Postapplication Exposure and Risk

Residential post-application exposures to flumethrin can also occur after collars are placed on a cat or dog via dermal and oral exposure routes. Residential postapplication inhalation exposure is expected to be negligible from flumethrin pet collars and thus a quantitative assessment was not performed. The durations of postapplication exposure relevant to the proposed use pattern are short-term, intermediate-term, and chronic as flumethrin pet collars could potentially be used year round. However, the available toxicological data supports the conclusion that neurotoxicity from flumethrin and pyrethroids in general is associated with acute, peak exposures. As such, only single day dermal risks were assessed. Dermal post-application risks were assessed for adults and children 1 < 2 years old while oral (hand-to-mouth) post-application risks were assessed for children 1 < 2 years old.

A pet transferable residue study (i.e., a petting study) was not submitted for flumethrin. Bayer did submit chemical-specific data (MRID 48240140 provides a summary of all of the data) related to the amount of flumethrin that was released from the small and large collars over the life of the collar (i.e., 8 months or 240 days). Depending on the study, measurements were taken at 30, 60, 90, and 240 days after applying the collar and these studies were performed on cats (small collars) and dogs (large collars). This data does not specifically provide the surface residues of flumethrin on a cat or dog nor does it provide the amount of flumethrin that could be transferred to a person who contacts a treated cat or dog. Since acute exposures are most toxicologically relevant for flumethrin, HED is most interested in flumethrin residues for the first few days after the collar is applied. The available studies did not collect any data from these days so for this assessment HED has focused only on the data that was collected at 30 days. Table 6.2a presents a summary of this data.

Table 6.2.a: Summary of Flumethrin Released from Small and Large Pet Collars (MRID 48240140)

Study Number	Collar Size	Study Period	Amount of Flumethrin Released Over Study Period (mg) [a]	Amount of Flumethrin Released per Day (mg/day) [b, c]	Average Flumethrin Released per Day (mg/day)
146.164	Small	30	42.43	1.41	0.94
146.747			13.7	0.46	
146.165	Large		87.49	2.92	2.39
146.737			55.9	1.86	

a. As summarized in MRID 48240140
b. Amount of flumethrin released per day (mg/day) = Amount of flumethrin released over study period (mg) / Study Period (days)
c. Assumes the release rate of flumethrin from the collar is consistent across the first 30 days

Using this data, along with some standard assumptions from the 2012 Treated Pet SOP (e.g., pet surface area, fraction of application rate available for transfer), HED estimated transferable residues by the equation presented below.

$$TR\ (mg/cm2) = \{[RR\ (mg/day) * 7\ days] / Animal\ SA\ (cm2)\} * F_{AR}$$

Where:

TR	=	Transferable Residue (mg/cm2)
RR	=	Release Rate (mg/day)
Animal SA	=	Animal Surface Area (cm2)
F_{AR}	=	Fraction Application Rate Available (F_{AR})

Because of the limitations of the available data, HED assumed the release rate of flumethrin from the collar was consistent across the first 30 days. However, pesticide release rates for pet collars are typically higher in the initial days and weeks after application. In order to be protective of this possibility, HED assumed that the Day 0 transferable residue would be the total of the first 7 days of released flumethrin. In addition to the estimated transferable residues, HED also used exposure algorithms (see Appendix C) and other standard assumptions (e.g., transfer coefficients, exposure time, fraction of pesticide on hands, hand-to-mouth events) taken from the 2012 Treated Pet SOP.

HED's levels of concern for residential postapplication adult and children exposures are equal to MOEs of 100 and 300, respectively. All residential postapplication dermal and incidental oral exposure scenarios do not exceed HED's level of concern (i.e., adult MOEs ≥ 100 and children MOEs ≥ 300). Postapplication dermal and incidental oral exposure and risks are summarized in Table 6.2.b and 6.2.c, respectively.

Table 6.2.b: Postapplication Dermal Exposure and Risk for Flumethrin

Animal Surface Area		TR [b] (mg/cm^2)	Transfer Coefficient (cm^2/hr)	ET (hrs)	BW (kg)	Dose [c] (mg/kg/day)	Dermal MOE [d]
Adults							
Small Cat	1,500	0.000087	5200	0.77	80	0.0044	2300
Large Cat	4,000	0.000033				0.0016	6100
Small Dog	3,000	0.000044				0.0021	4600
Medium Dog	7,000	0.000048				0.0024	4200
Large Dog	11,000	0.000030				0.0015	6600
Children (1 < 2 years old)							
Small Cat	1,500	0.000087	1500	1	11	0.012	870
Large Cat	4,000	0.000033				0.0045	2200
Small Dog	3,000	0.000044				0.0060	1700
Medium Dog	7,000	0.000048				0.0065	1500
Large Dog	11,000	0.000030				0.0041	2400

a. Small cat TR= [(0.94 mg/day * 7 days) / 1500 cm^2] * 2%
Large cat TR= [(0.94 mg/day * 7 days) / 4000 cm^2] * 2%
Small dog TR= [(0.94 mg/day * 7 days) / 3000 cm^2] * 2%
Medium dog TR= [(2.39 mg/day * 7 days) / 7000 cm^2] * 2%
Large dog TR= [(2.39 mg/day * 7 days) / 11000 cm^2] * 2%
b. Dermal Dose (mg/kg/day) = TR (mg/cm2) * TC (cm^2/hr) * ET (hrs) / BW (kg)
c. Dermal MOE = NOAEL (10 mg/kg/day)/Dermal Dose

Table 6.2.c: Postapplication Incidental Oral (Hand-to-Mouth) Exposure and Risk for Flumethrin												
Dermal Exposure (mg)		Fai_{Hands}	SA Hands (cm^2)	HR [a] (mg/ cm^2)	FM (fraction/ event)	ET (hrs)	N_replen	SE	$Freq_{HtM}$	BW (kg)	Dose [b] (mg/kg/day)	Oral MOE [c]
Small Cat	0.14	0.039	150	0.000018	0.13	1	4	0.48	20	11	0.00012	4300
Large Cat	0.051			0.0000066							0.000045	11000
Small Dog	0.068			0.0000088							0.000058	8600
Medium Dog	0.074			0.0000097							0.000064	7900
Large Dog	0.047			0.0000061							0.000041	12000

a. $[HR = DE * Fai_{hands}] / 2 * SA_H$
b. Oral Dose = $[HR * (F_M * SA_H) * (ET * N\_Replen) * (1- (1- SE)^{(Freq\_HtM/N\_Replen)})] / BW$
c. Oral MOE = NOAEL (0.5 mg/kg/day)/Dermal Dose

6.3 Combined Residential Risk Estimates

HED combines risk values resulting from separate exposure pathways when it is likely they can occur simultaneously based on the use pattern, the behavior associated with the exposed population, and the hazard associated with the points of departure. For flumethrin, the points of departure are based on different effects and thus it is not appropriate to combine the dermal and oral exposure scenarios.

7.0 Aggregate Exposure/Risk Characterization

There are currently no registered food uses for flumethrin and drinking water exposure is not expected from the proposed pet collar uses of flumethrin; therefore, a quantitative aggregate risk assessment is not required at this time.

8.0 Cumulative Exposure/Risk Characterization

The Agency is required to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The Agency has determined that the pyrethroids and pyrethrins share a common mechanism group (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). The members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. The cumulative risk assessment for the pyrethroids/pyrethrins was published on Nov. 9, 2011 (USEPA, 2011a) and is available at http://www.regulations.gov; EPA-HQ-OPP-2011-0746. No cumulative risks of concern were identified allowing the Agency to consider new uses for pyrethroid actives. For information regarding EPA's efforts to evaluate the risk of exposure to pyrethroids, refer to http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.

As a new active ingredient, flumethrin was not currently included in the initial common mechanism grouping (CMG) science policy document from 2008 and was not assessed in the November 2011 pyrethroid cumulative risk assessment. However, the Agency has determined based on its chemical structure and based on the observation of neurobehavioral effects consistent with Type II pyrethroids, that flumethrin should be included in the CMG for this class of pesticides. As such, the Agency must consider the potential contribution of flumethrin to the cumulative risk assessment. As part of the assessment for the proposed flumethrin pet collar

uses, the Agency performed a quantitative analysis and determined that the proposed flumethrin pet collar use will not significantly contribute to or change the overall findings in the pyrethroid cumulative risk assessment. That analysis is summarized in Appendix D.

9.0 Occupational Exposure/Risk Characterization

Based on the proposed flumethrin pet collar uses, there is potential for both occupational handler and occupational post-application exposure to occur.

9.1 Occupational Handler Exposure and Risk

For the proposed flumethrin pet collar uses, occupational handler exposures are expected to be less or at worst case equal to the residential handler exposures as this is traditionally considered a consumer product as opposed to one applied by veterinarians or professional groomers. As a result, no quantitative occupational handler exposure and risk assessment has been performed. The residential handler exposure and risk assessment (see Section 6.1) is considered protective for any potential occupational handler exposures and risks.

9.2 Occupational Post-Application Exposure and Risk

For the proposed flumethrin pet collar uses, occupational post-application exposure could potentially occur; however, these types of exposures are not expected to be greater than residential post-application exposures (i.e., minimal and infrequent contact by a professional animal care worker is expected to occur after a collar is applied). As a result, no quantitative occupational post-application exposure and risk assessment has been performed. The residential post-application exposure and risk assessment (see Section 6.2) is considered protective for any potential occupational post-application exposures and risks.

10.0 References

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Appendix A: Flumethrin Toxicity Profiles

A.1 Toxicology Data Requirements

Guideline Number and Toxicity Study		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	no
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Sub-chronic (Rodent)	CR	yes
870.3150	Oral Sub-chronic (Non-Rodent)	CR	no
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	yes	yes
870.3465	90/28-Day Inhalation	CR	yes
870.3700	Developmental Toxicity (Rodent)	yes	yes
870.3700	Developmental Toxicity (Non-rodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100	Chronic Toxicity (Rodent)	CR	no
870.4100	Chronic Toxicity (Non-rodent)	no	yes
870.4200	Oncogenicity (Rat)	CR	no
870.4200	Oncogenicity (Mouse)	CR	yes
870.4300	Chronic/Oncogenicity	CR	yes
870.5100	Mutagenicity: Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity: Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity: Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity: Structural Chromosomal Aberrations	yes	yes
870.5500	Mutagenicity: Other Genotoxic Effects	yes	yes
870.5550	Mutagenicity: Other Genotoxic Effects	yes	no
870.6100	Acute Delayed Neurotoxicity (Hen)	CR	--
870.6100	90-Day Neurotoxicity (Hen)	CR	--
870.6200	Acute Neurotoxicity Screening Battery (Rat)	yes	yes
870.6200	90 Day Neuro. Screening Battery (Rat)	yes	yes
870.6300	Developmental Neurotoxicity	CR	yes
870.7485	General Metabolism	CR	yes
870.7600	Dermal Penetration	CR	no
870.7800	Immunotoxicity	yes	yes

--Not applicable

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Appendix A.2. Toxicity Profiles

Table A.2.1: Acute Toxicity Profile – Flumethrin (PC 036007)

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral, rat	48240203	LD_{50} Females = 175 mg/kg	II
870.1100	Acute oral, rat	48240204	LD_{50} Males > 100 mg/kg LD_{50} Females = 100 mg/kg	II
870.1200	Acute dermal, rat	48240206	LD_{50} Males = 1998 mg/kg LD_{50} Females = 1436 mg/kg	II
870.1300	Acute inhalation, rat	48240208	LC_{50} Males > 0.585 / <0.812 mg/L LC_{50} Females > 0.277 / <0.585 mg/L	II
870.2400	Acute eye irritation, rabbit	48240211	Waiver requested	IV
870.2500	Acute dermal irritation, rabbit	48240213	Slight irritant; PII=0.25 Bruising observed one animal at 1 hr.	IV
870.2600	Skin sensitization, guinea pig	48240214	Not Determined	Unacceptable

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.3100	Subchronic (Oral) Toxicity - Rodent	48240222 (1995) rat Acceptable/guideline 0, 10, 40, 160 ppm (rat) M: 0, 0.7, 2.9, or 11.9 mg/kg/day F: 0, 0.8, 3.4, 13.0 mg/kg/day	NOAEL- 0.7/0.8 mg/kg/day (M/F) LOAEL – 2.9/3.4 mg/kg/day (M/F), ↑extramedullary hematopoiesis; ↓hemosiderin storage; labored breathing; ↑salivation (F); shoulder wounds (M)
		48240224 (1998) mice Acceptable/guideline (mice) 0, 5, 10, **60, 120, 240, 480** ppm **(95.1%, T0059204)** M: 0, 9.9, 20.8, 42.2 mg/kg/day F: 0, 13.2, 26.5, 56.0 mg/kg/day (94.4%, T4060297) M: 0, 0.9, 1.9 mg/kg/day F: 0, 1.4, 2.5 mg/kg/day	NOAEL - 0.9/1.9 (M/F) LOAEL - 1.4/2.5 mg/kg/day, piloerection, dermal lesions, mild hyperkeratosis and acanthosis, emaciation, and mortality at higher doses
870.3250	90 Day Dermal Toxicity - Rat	48240216 (2008) Acceptable/guideline 0, 10, 30, or 80 mg/kg/day	NOAEL - 10 mg/kg/day LOAEL - 30 mg/kg/day, loss of hair; ↓BW and ↓BWG (M), ↓erythrocytes, high stepping gait, ↓ABS spleen wt
870.3200	28 Day Dermal Toxicity - Rat	48240217 (2006) Acceptable/non-guideline 0, 100, 150, 200 mg/kg/day	NOAEL – not established, insufficient number of animals. Clinical signs: bloody muzzle, sunken flanks, reduced motility, high-stepping gait, labored breathing, diarrhea, narrowed eyelids, ↑salivation
	14 Day Dermal Toxicity - Rat	48240218 (2007) Acceptable/non-guideline 0, 10, 30, 100 mg/kg/day	NOAEL – not established, insufficient number of animals. Clinical signs: bloody muzzles, bleedings on nose, hunched backs, reduced motility, high-stepping gait, labored breathing, narrowed eyelids, ↑salivation
870.3700a	Prenatal Developmental Toxicity - Rat	48240225 (1999) Acceptable/guideline 0, 0.75, 2, 5 mg/kg/day	**Maternal** NOAEL – 0.75 mg/kg/day. LOAEL - 2 mg/kg/day, ↓ *H2O, ↓feces, ↓BW/BWG, ↓gravid uterine wt, ↓food consumption*; ↓BW **Developmental** NOAEL – 2 mg/kg/day. LOAEL - 5 mg/kg/day, ↓BW , ↓placenta wt retardation/ossification/microphthalmia
870.3700b	Prenatal Developmental Toxicity – (Rabbit)	48240226 (2009) Acceptable/guideline 0, 0.5, 1.5, 4.5 mg/kg/day	**Maternal** NOAEL – 1.5 mg/kg/day. LOAEL – 4.5 mg/kg/day, Abortions, cold ears, hind limb swelling, soft feces, ↓H2O, ↓urine, enlarged gall bladder, encrusted wounds at throat/forelimbs **Fetal** NOAEL – 1.5 mg/kg/day. LOAEL – 4.5, retarded ossification of metacarpals, phalanges, 1st cervical vertebrae
870.3800	Reproduction and Fertility Effects	48240227 (2008) 0, 0.5, 1, 3 mg/kg/day Acceptable/guideline Gavage	**Parental** NOAEL not established (M) LOAEL - 0.5 mg/kg/day ↓pituitary in F1 (15%) NOAEL - 0.5 (F) LOAEL - 1.0 mg/kg/day ↓liver weights in F0 & F1 **Reproductive** NOAEL - 3.0 mg/kg/day HDT **Offspring** NOAEL - 1.0 mg/kg/day M/F LOAEL - 3.0 mg/kg/day thinness, no milk spots, ↓BW, ↓rearing indexes with ↑deaths at PND 0-4.

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
		48240228 (1992) Acceptable/guideline 0, 1, 5, 50 ppm M: 0, 0.05, 0.23, 2.42 mg/kg/day F: 0, 0.06, 0.28, 2.92 mg/kg/day Dietary	**Parental** NOAEL = 0.23 mg/kg LOAEL = 2.42 mg/kg ↓body weight gain in P generation (males), ↓body weight and food consumption in (females) during lactation, ↑postnatal loss in all generations, ↓food consumption in P and F1 males, ↓body weight gain in male and female pups in all generations **Reproductive** NOAEL = 2.42 mg/kg HDT **Offspring** NOAEL ~ 0.23 mg/kg. LOAEL = 2.42 mg/kg ↓body weight and body weight gains in males and female pups, significantly different testes and ovaries weight, ↓ survival at 21 days
870.3465	Inhalation Toxicity	48240219 (1997) Acceptable/guideline 0.1, 1.4, 20.0 mg/m^3 Analytical 0.12, 1.33 and 22.4 mg/m^3	NOAEL = 0.12 mg /m^3 LOAEL = 1.33 mg /m^3 based on the results from clinical signs of toxicity battery of reflex tests and lung function measurements, hematology and clinical chemistry. bradypnea, labored breathing, red discharge or encrustations from the perinasal area. Sporadically, in females decreased motility, atony, and salivation. Signs resolved during the days of no exposure.
870.4200	Carcinogenicity - Mouse	48240223 (1999) Acceptable/guideline 0, 1,3, 15, 30 ppm M: 0, 0.12, 0.39, 1.97, 4.56 mg/kg/day F: 0, 0.15, 0.52, 2.54, 4.95 mg/kg/day	NOAEL ~ 0.39/0.52 (M/F) mg/kg/day LOAEL – 1.97/2.54 (M/F) mg/kg/day, ↑skin discoloration, incrustations, sores, missing/deformed ears, epidermal hyperplasia, inflammation, ulceration, M= enlarged/swollen spleens, ↑plasmacytosis mandibular LN, hematopoiesis BM, ↑reduced liver glycogen and hepatocytic atrophy (salivation seen at higher doses, 60ppm↑) There were no increased incidences of treatment related tumors compared to controls
870.4300	Combined Chronic Toxicity/ Carcinogenicity - Rat	42820221 (1999) Acceptable/guideline 0, 0.7, 2, 4 mg/kg/day	NOAEL ~ 0.7 mg/kg/day LOAEL ~ 2 mg/kg/day Severe skin lesions, enlarged LN/swollen spleens, plasmacytosis, ↑adrenal cortex vacuolation, no treatment related tumor incidence compared to controls
870.6200a	Neurotoxicity Screening Battery - Acute - Rat	48240215 (2008) Acceptable/guideline 0, **0.25, 0.50**, 1, 5, 15 mg/kg	NOAEL – 0.5 mg/kg/day in **males** LOAEL – 1.0 (M/F) mg/kg/day, ↓motor/locomotor activity, ↑staining of mouth, perianal, nose, ↑lacrimation, salivation at ↑doses
870.6200b	Neurotoxicity Screening Battery - Subchronic - Rat	48240220 (2008) Acceptable/ guideline 0,1, 2.5, 5 mg/kg/day	NOAEL – 1 mg/kg/day LOAEL – 2.6 mg/kg/day, ↓food consumption, BW/BWG males only, urine/lacrimal/perianal/oral stains, ↓figure8 maze activity (Salivation seen at higher doses)

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.6300	Neurotoxicity Developmental	48240232 (2008) Acceptable/guideline 0, 0.5, 1, 2 mg/kg/day	**Maternal** NOAEL – 1 mg/kg/day LOAEL- 2 mg/kg, BW/day for maternal animals and offspring, based on ↓body weight (-3%) and body weight gain (-9%, p<0.05), and ↓food consumption (-15%, p<0.05, in dams only). Salivation also seen. **Offspring** NOAEL – 1mg/kg/day LOAEL- 2 mg/kg, ↓ BW in M on PND 11 and 17 (- 8%, p<0.01) and in the low and high dose F on PND 11 (-6%, p<0.05) and were associated with significant reduced body weight gain that began on PND 4-11. In addition, body weight was non-statistically decreased on PND 21 in M. This difference in body weight for males persisted to study termination (statistically decreased 6-7% compared to control).
870.5100	Bacterial Reverse Mutation Test	48240233 (1993) Acceptable/guideline 0, 8, 40, 200, 1000, and 5000 µg/plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240234 (1993) Unacceptable/non-guideline 0, 7500, 10,000, 12,500, 15,000 µg/plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240235 (2006) Acceptable/guideline 0, 16, 50, 158, 500, 1581 and 5000 ug/per plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5300	In vitro mammalian cell gene mutation test	48240236 (1995) Acceptable/guideline 0, 6.25, 12.5, 25, 50, 75, and 100 µg/mL (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240237 (2007) Acceptable/guideline 0, 25, 50, or 100 µg/mL	There was no evidence of chromosomal aberrations. [Negative]
		48240239 (2007) Acceptable/guideline 0, 6, 12, 24, 48, 96 or 182 µg/mL	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5375	In vitro mammalian chromosome aberration test	48240238 (1995) Acceptable/guideline 100, 200, 500, 1000, 2500, or 5000 µg/mL (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5395	Mammalian erythrocyte micronucleus test	48240240 (2007) Acceptable/guideline 0, 125, 250, 500 mg/kg	This chemical was not found to be clastogenic or aneugenic. [Negative]

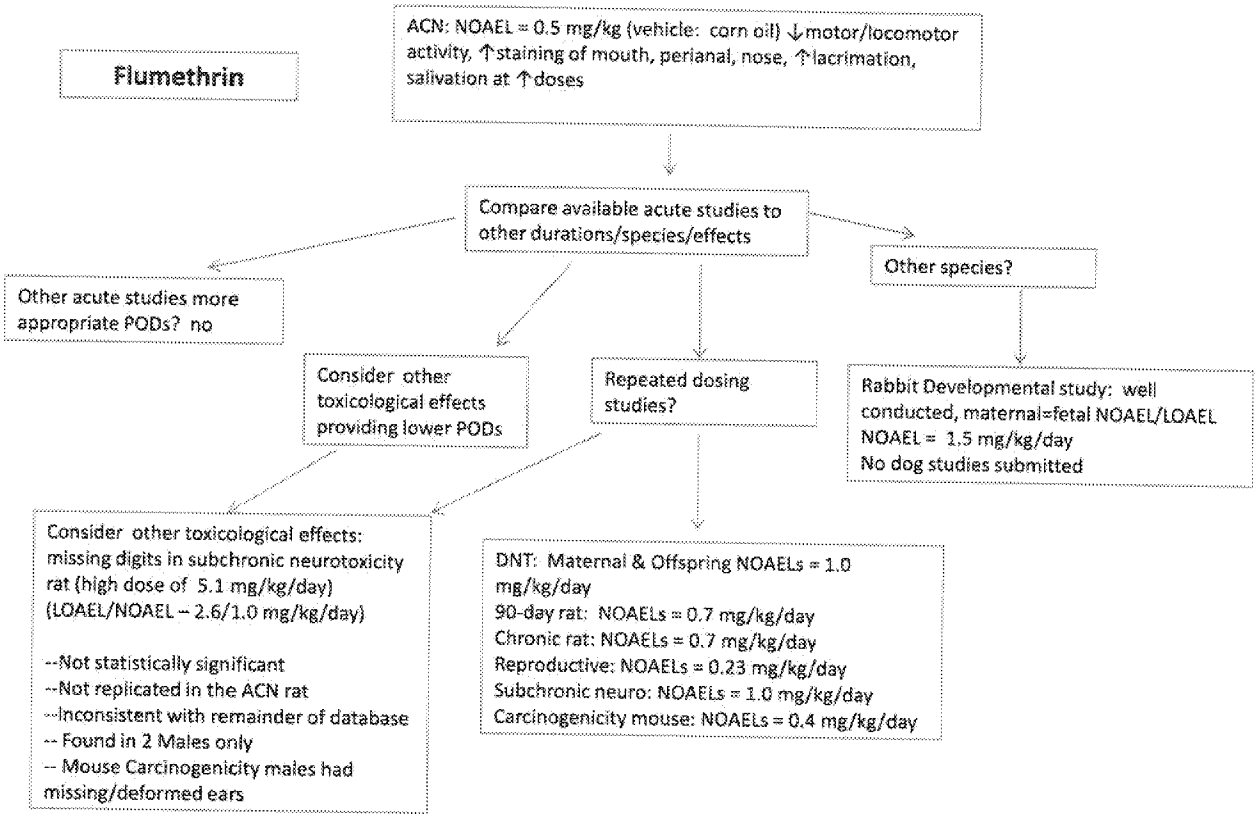
Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
		48240241 (1995) Acceptable/guideline 0, 1000mg/kg	There was no evidence of chromosomal aberrations with or without activation. [Negative]
870.5500	Unscheduled DNA Synthesis *in vitro*	48240242 (1994) Acceptable/guideline 0, 5, 10, 50, 100, 200, 300, 500 µg/mL	There was no evidence of genotoxic activity. [Negative]
870.7485	Metabolism and pharmacokinetics	48240243 (1992) Acceptable/guideline 1, 5 mg/kg	Radioactivity administered with [Cl-phenyl-U-^{14}C] flumethrin was rapidly but incompletely absorbed from the intestinal lumen of rats. Excretion of the compound was slow and mostly in the feces comprising 77-88 % of the dose. The majority of the radioactive feces eliminated had been absorbed and excreted with the bile into the gut lumen. The highest amount of radioactivity in the body was mainly found in the plasma, which at sacrifice showed the highest residue concentration in dose groups tested. All other organs exhibited significantly lower concentrations. The lowest values were determined in the brain, indicating that the blood-brain barrier is almost impermeable for the test compound and its labeled metabolites. The radioactive residues in the body excluding the gastrointestinal tract at sacrifice, seven days after dosing, were still relatively high, varying between 9 % and 20 % of the given dose. The multiple dose experiment clearly showed an accumulation of the radioactivity in the body. The 24 hour dosing interval was too short to completely allow for the elimination of the administered radioactivity. Since the renal excretion played only a negligible role, metabolite identification was conducted exclusively in the feces.
		48240244 (2000) Acceptable/non-guideline 0, 50, 160ppm	Mean plasma concentration of flumethrin and flumethrin granules after 3, 6, 13 weeks of 160ppm were bioavailability were similar
870.7800	Immunotoxicity	48240250 (2009) Acceptable/guideline 0, 10, 40, 160 ppm 0, 0.8, 3, 11.7 mg/kg/day M 0, 1, 3.5, 12.3 mg/kg/day F	Systemic NOAEL- 3/3.5 LOAEL-11.7/12.3 (M/F) ↓BW (significant in week 1 only for F)

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
Non-guideline	4-week Gavage Pilot, for 2-Gen rat repro	48240229 (2006) Acceptable/non-guideline 5.0, 7.5,10.0 mg/kg/day	Males NOAEL- Not established. LOAEL = 5 mg/kg/day (HDT) ↓reduced mean relative spleen and thymus weights and ↓absolute thymus and spleen weight. Females LOAEL - 10 mg/kg/day slightly ↓ mean body weight and reduced mean absolute and spleen weights Female NOAEL = 7.5 mg/kg/day
Non-guideline	Rat Plasma – Gavage, 2 –Gen rat repro	48240245 (2007) Acceptable/non-guideline 0, 0.5, 1.0, or 3.0 mg/kg/day	Plasma concentration study, a part of the 2-generation reproduction study no. (MRID 48240227), The animals were grouped into one control and 3 dose groups per sex and generation. All results for control group animals were below the limit of quantification. Results obtained from rats in the various dose groups showed a clear dose-concentration relation. The highest concentrations were found four hours after dosing. The concentration results for male animals were significant higher than for females.
Non-guideline	Rat Plasma – Pilot with MRID 48240230	48240231 (2006) Acceptable/non-guideline 0.08, 0.4 or 2 mg/kg/day	This study was part of an exploratory subchronic oral toxicity study (MRID 48240230) in which plasma was collected from male and female rats and analyzed to determine plasma concentrations of flumethrin. Maximum plasma levels were measured at 2 to 4 hours after administration at each dose level. At the dose concentration between 0.4 and 2.0 mg/kg there was a clear increase of plasma levels with dose that was visible in both sexes. Continuing plasma level increases were not seen in the dosage range of 3.0 to 5.0 mg/kg (after enhanced dose scheme).
Non-guideline	19-week Gavage Pilot, for 2-Gen rat repro	48240230 (2006) Acceptable/non-guideline 0, 0.08, 0.4, 2.0 mg/kg/day After day 70: 3, 4, 5 mg/kg/day	**Parental male** NOAEL- 3 mg/kg/day LOAEL - 4 mg/kg/day ↓slightly body weight. **Parental female** NOAEL - 2 mg/kg/day lack of effects prior to dose elevation LOAEL- 3 mg/kg/day ↓bw during pregnancy. **Offspring** NOAEL –2 mg/kg/day LOAEL = 3 mg/kg/day The body weight changes were insignificant for M/F. ↑absolute adrenal wt in F ($p<0.01$) and ↓thymus weight in males- 3, 4 mg/kg/day.

Appendix A.3. Hazard Identification and Endpoint Selection

mg/kg/day	SC rat	CC rat	DNT	SC mouse	CC mouse	DT rat	DT rabbit	repro/2-gen	repro/2-gen	Dermal r	SCN	ACN	Immuno
MRID	48240222	48240221	48240232	48240224	48240223	48240225	48240226	48240227 (G)	48240228 (D)	48240216	48240220	48240215	48240250
0													
0.2													
0.4					NOAEL-M				NOAELp/o				
0.6		NOAEL										NOAEL	
0.8	NOAEL-M			NOAEL-M		NOAELm		LOAEL-M NOAELf					
1			NOAELm/o					NOAELo LOAELf			NOAEL		
1.5				LOAEL-M			NOAELm/d					LOAEL	
2		LOAEL	LOAELm/o		LOAEL-M	LOAELm NOAELd							
2.5									NOAEL r (HDT) LOAEL p/o				
3	LOAEL-M										LOAEL		
3.5								LOAELo NOAEL r					NOAEL
4													
4.5							LOAEL m/d						
5						LOAELd							
10										NOAEL			NOAEL LOAEL
20													
30													
40										LOAEL			
50													
80													
90													
100													
150													
200													

m = maternal; d = developmental; p = parental; o = offspring; r = reproductive; s = systemic; n = neurotoxic; f= female; M=male



A.3.1 Acute Reference Dose (aRfD) - Females age 13-49

A.3.2 Acute Reference Dose (aRfD) - General Population

Acute dietary endpoints were available to quantify risk to the general population, including infants and children. However, no PODs were chosen since the exposure scenarios did not warrant such values to be assessed.

A.3.3 Chronic Reference Dose (cRfD)

Chronic endpoints have not been chosen for flumethrin since the exposure scenarios did not warrant such values to be assessed.

A.3.4 Incidental Oral Exposure (Short-Term)

The NOAEL of 0.5 mg/kg/day from the acute neurotoxicity study is selected for this endpoint due to the overall consistency of the database and the exposure scenario of this study. The POD identified in the ACN study is found to be protective and captures the dose spread for the 2-generation reproductive study which has a lower identified NOAEL (0.23 mg/kg/day). The Hazard Identification and Endpoint Selection graph A.3 portrays the nearly flat dose-response for does which elicit many of the clinical signs seen in the database, and moreover, within these two studies. There were clear signs of increased salivation, lacrimation, and decreased motor and locomotor activity in both sexes at the LOAEL of 1.0 mg/kg /day. Therefore, the exposure scenario combined with the overlap in doses which produced an adverse effect due to treatment

within the acute neurotoxicity study gave more confidence in the data.

A.3.5 Dermal Exposure (Short-Term)

The 90-day dermal study in rats with NOAEL of 10 mg/kg/day was selected for this endpoint. The LOAEL value of 30 mg/kg/day was based on observations of clinical signs (high stepping gait), and decreased body weight and weight gain. Since a dermal toxicity study is selected for dermal risk assessment, a dermal-absorption factor is not required.

A.3.6 Inhalation Exposure (Short-Term)

An inhalation study was available to quantify risk to the general population and deemed acceptable. However, no PODs were chosen since the exposure scenarios did not warrant such values to be assessed.

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Appendix A.4. Human Equivalent (dog study vs. acute rat motor activity)

RAT (Wolansky)					DOG (Subchronic)			
chemical	rat dose (mg/kg)		human dose (mg/kg)		dog dose (mg/kg)		human dose (mg/kg)	
	BMD	BMDL	BMD	BMDL	NOAEL	LOAEL	NOAEL	LOAEL
beta-cyfluthrin	1.42	1.17	0.412816	0.340137	2.4	13.9	1.475491567	8.545555
bifenthrin	4.1	3.1	1.191933	0.9012176	2.2	4.2	1.352533936	2.58211
bioallethrin	65.6	42.2	19.07093	12.268189				
cyhalothrin	0.92	0.64	0.267458	0.1860578	1	2.5	0.614788153	1.53697
cyphenothrin					12.5	37.5	7.684851912	23.05456
cypermethrin	11.19	7.16	3.253105	2.081522	12.5	37.5	7.684851912	23.05456
deltamethrin	2.48	1.49	0.720974	0.4331659	1	2.5	0.614788153	1.53697
esfenvalerate	1.19	0.65	0.345951	0.188965	5	7.5	3.073940765	4.610911
fenpropathrin	6.44	5.01	1.872207	1.456484				
permethrin	63.1	44.4	18.34414	12.907762	50	500	30.73940765	307.3941
resmethrin	162.32	75.89	47.18892	22.062389				
tefluthrin	3.67	2.8	1.066925	0.814003				

Rat BW (kg) = 0.5
Dog BW (kg) = 10
Human BW (kg) = 70

Appendix B: Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. These studies, which have been utilized in the 2012 Treated Pet SOP, have been determined to require a review of their ethical conduct, have received that review, and have been determined to be ethical.

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Appendix C: Residential Exposure Algorithms and Standard Inputs

C.1. Residential Handler

Exposure Algorithms

Daily dermal and inhalation exposure (mg/day) for residential pesticide handlers, for a given formulation-application method combination, is estimated by multiplying the formula-application method-specific unit exposure by an estimate of the amount of active ingredient handled in a day, using the equation below:

$$E = UE * AR * A$$

where:

E	= exposure (mg/day);
UE	= unit exposure (mg/lb ai);
AR	= application rate (lb ai/pet); and
A	= number of animals treated per day.

Absorbed dermal and/or inhalation dose normalized to body weight is calculated as:

$$D = \frac{E * AF}{BW}$$

where:

D	= dose (mg/kg-day);
E	= exposure (mg/day);
AF	= absorption factor (dermal and/or inhalation); and
BW	= body weight (kg).

Standard Handler Algorithm Inputs

Dermal Unit Exposure Summary: No dermal exposure data are available for application of pet collars. Exposure data for spot-on applications to pets are recommended for use as surrogate data. The recommended dermal unit exposures for spot-on applications to pets or animals is based on a lognormal distribution fit with exposure monitoring data from Meo, N., et al (1997) [EPA MRID 44433303]. Meo, N., et al (1997) monitored 16 applications by commercial pet groomers to 8 dogs for approximately 14-32 minutes using a ready-to-use (RTU), disposable, snap-top, plastic-backed pipette. The dermal unit exposure is 120 mg/lb ai.

Inhalation Unit Exposure Summary: Ihalation exposure for application of pet collars is considered to be negligible.

Number of Animals Treated: It is assumed that residential handlers of pet treatment products will treat 2 animals per application (N). This estimate is based upon information available from The

Humane Society of the United States[2] which references data from the American Pet Products Manufacturers Association (APPA) 2011-2012 National Pet Owners Survey that reports pet owners have an average of 1.7 dogs and 2.2 cats.

C.2. Residential Post-application

Exposure Algorithms

Post-application Dermal Exposure Algorithm: The following method is used to calculate dermal exposures that are attributable to an adult or child contacting a treated companion pet:

$$E = TC * TR * ET$$

where:

E = exposure (mg/day);
TC = transfer coefficient (cm^2/hr);
TR = transferable residue (mg/cm^2); and
ET = exposure time (hours/day).

$$TR = \frac{AR * F_{AR}}{SA}$$

where:

TR = transferable residue (mg/cm^2);
AR = application rate or amount applied to animal (mg);
F_{AR} = fraction of the application rate available as transferable residue; and
SA = surface area of the pet (cm^2).

Absorbed dermal dose, normalized to body weight, is calculated as:

$$D = \frac{E * AF}{BW}$$

where:

D = dose (mg/kg-day);
E = exposure (mg/day);
AF = absorption factor (dermal); and
BW = body weight (kg).

Post-application Hand-to-Mouth Exposure Algorithm: Exposure from hand-to-mouth activity is calculated as follows (based on algorithm utilized in SHEDS-Multimedia):

[2] http://www.humanesociety.org/issues/pet_overpopulation/facts/pet_ownership_statistics.html

$$E = [HR * (F_M * SA_H) * (ET * N\_Replen) * (1 - (1 - SE)^{(Freq\_HtM/N\text{-}Replen)})]$$

where:

E	= exposure (mg/day);
HR	= hand residue loading (mg/cm^2);
SA_H	= surface area of one child hand (cm^2);
F_M	= fraction hand surface area mouthed /event (fraction/event);
ET	= exposure time (hr/day);
N_Replen	= number of replenishment intervals per hour (intervals/hour);
SE	= saliva extraction factor (i.e., mouthing removal efficiency); and
Freq_HtM	= number of hand-to-mouth contacts events per hour (events/hour).

and

$$HR = \frac{E * Fai_{hands}}{2 * SA_H}$$

where:

HR	= hand residue loading (mg/cm^2);
E	= dermal exposure (mg);
Fai_{hands}	= fraction of a.i. on hands compared to total residue from dermal transfer coefficient study (unitless); and
SA_H	= surface area of one child hand (cm^2).

Oral dose, normalized to body weight, is calculated as:

$$D = \frac{E}{BW}$$

where:

D	= dose (mg/kg-day);
E	= exposure (mg/day); and
BW	= body weight (kg).

Standard Post-application Algorithm Inputs

Transfer Coefficient (TC): The transfer coefficients used for pet exposure were derived from two studies representing application and grooming activities with dogs, one using a carbaryl shampoo product (Mester, 1998) and the other using a carbaryl dust product (Merricks, 1997); these are used to represent TCs for liquid and solid formulations, respectively. Data were gathered while human volunteers applied pet pesticide products to various dogs of differing sizes and fur lengths. The information identified best approximates the exposures that could occur from interactions with treated pets because these studies included the direct measurement of exposures to applicators or pet groomers. Since these individuals directly handled pesticide products and had direct contact with treated pets, it is expected that their resulting exposures are a reasonable approximation of upper bound estimates of contact with a treated animal. In the absence of direct exposure data for this scenario (e.g., homeowner activity with a treated pet), the Agency assumes that the application and grooming activities are likely to result in a protective estimate

of exposure than just the evaluation of petting, hugging or sleeping with a pet. A TC of 5,200 cm^2/hr for adults and 1,400 cm^2/hr for children is recommended for addressing all durations of post-application exposure for all liquid formulations (or formulations that behave as liquids) including RTU liquid formulations (i.e., aerosol/trigger sprays, dips, pet collars, shampoos and spot-ons).

Fraction Application Rate (F_{AR}): If chemical specific transferable residue measurements are not available, then a standard value for the fraction of active ingredient available (F_{AR}) for transfer is used. In this SOP, a screening level F_{AR} was recommended based on the review of 8 pet residue transfer, or "petting," studies (9 data sets total) submitted to the Agency. Measurements of residue transfer were derived by taking the ratio of the amount of active ingredient on a bare or gloved hand (on the day of highest observed transfer) to the amount of active ingredient applied. Five residue transfer studies were performed by means of volunteers "petting" or "stroking" animals treated with a known amount of active ingredient. Three additional residue transfer studies were conducted using a gloved mannequin hand. For each study the amount of residue transferred to the hands was determined. Based on the available pet residue transfer studies, the recommended screening level F_{AR} point estimate for use in post-application dermal exposure assessment is 0.02 (equivalent to 2%).

Exposure Time (ET): The exposure time (ET) for pets for adults and children was derived from Tsang and Klepeis, 1996 (as presented in 1997 Exposure Factors Handbook Table 15-77). Animal care is defined in the 1997 Exposure Factors Handbook as "care of household pets including activities with pets, playing with the dog, walking the dog and caring for pets of relatives, and friends." The data identified the time spent with an animal while performing household activities as recorded in 24 hour diaries by study volunteers. While the activities defined do not necessarily represent the time volunteers were actively engaged in constant contact with the animal as is implicit in the post-application dermal and incidental oral algorithms, the data are the most accurate representation of time spent with pets available and, therefore, it is assumed that contact is continual throughout the timed activity. The recommended point estimate for use in post-application dermal exposure assessments is 1.0 hour for children and 0.77 hours for adults.

Surface Area (SA): Animal surface area (SA) is determined by inputting animal weight (lbs) into an algorithm (12.3*((animal body weight (lbs)*454)^0.65)) as referenced from U.S. EPA (1993) Wildlife Exposure Factors Handbook. Representative surface areas have been calculated for the assigned cat and dog weight ranges. The surface areas for assessment are as follows:

- Cats – Small (1500 cm^2), Medium (2500 cm^2) and Large (4000 cm^2).
- Dogs – Small (3000 cm^2), Medium (7000 cm^2) and Large (11000 cm^2).

Fraction Active Ingredient on the Hands (Fai_{hands}): The fraction of active ingredient available on the hands was based on the two dermal pet transfer coefficient studies that represent application and grooming activities with dogs and used to derive dermal TCs. One study used a carbaryl shampoo product (Mester, 1998) and the other a carbaryl dust product (Merricks, 1997). These values were determined for liquid and solid formulations, respectively, by taking the average fraction of active ingredient on the hands and comparing that value to the average fraction of

active ingredient on the entire body. This analysis resulted in values of 4% for liquid formulations and 37% for solid formulations.
Fraction Hand Surface Area Mouthed (F_M): The recommended F_M value for use in post-application non-dietary ingestion exposure assessments is 0.13.

Hand Surface Area (SA_H): The hand surface area for children 1 < 2 years old of 150 cm^2, for one hand, was based on values from the Exposure Factors Handbook 2011 Edition (U.S. EPA, 2011).

Replenishment Intervals per Hour (N_Replen): This SOP assumes an estimate of 4 replenishment intervals per hour (i.e., residues on the hand will be replenished every 15 minutes). This value was selected as a conservative assumption based on the use of 30 minutes in the SHEDS model to coincide with the CHAD diaries.

Fraction of Pesticide Extracted by Saliva (SE_H): The recommended value for use in post-application non-dietary ingestion exposure assessments is 0.48.

Hand-to-Mouth Events per Hour (Freq_HtM): Frequency of hand-to-mouth events is an important variable for post-application non-dietary ingestion exposure assessments. However, there are currently no data available that specifically address the number of hand-to-mouth events that occur relative to the amount of time a child spends with a pet. As a result, the estimates for frequency of hand-to-mouth events in indoor environments from the Xue et al. (2007) meta-analysis were used as a surrogate. The indoor data were selected, even though child exposure to treated pets can occur either indoors or outdoors, because the indoor data result in a greater frequency of contacts. Therefore, using these data are the most conservative and thus the most health protective estimate of exposure. The recommended point estimate for use in post-application non-dietary exposure assessments is 20 for children 1 < 2 years old.

Appendix D: Pyrethroid Cumulative Screen

The Agency is required to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The Agency has determined that the pyrethroids and pyrethrins share a common mechanism group (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). The members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. The cumulative risk assessment (CRA) for the pyrethroids/pyrethrins was published on Nov. 9, 2011 (USEPA, 2011a) and is available at http://www.regulations.gov; EPA-HQ-OPP-2011-0746. No cumulative risk estimates of concern were identified allowing the Agency to consider new uses for pyrethroid actives. For information regarding EPA's efforts to evaluate the risk of exposure to pyrethroids, refer to http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.

As a new active ingredient, flumethrin was not included in the initial common mechanism grouping (CMG) science policy document from 2008 and was not assessed in the November 2011 pyrethroid cumulative risk assessment. However, the Agency has determined based on its chemical structure and based on the observation of neurobehavioral effects consistent with Type II pyrethroids, that flumethrin should be included in the CMG for this class of pesticides. As such, the Agency must consider the potential contribution of flumethrin to the cumulative risk assessment. As part of the assessment for the proposed flumethrin pet collar uses, the Agency has performed an analysis to determine if the use will significantly contribute to or change the overall findings in the pyrethroid CRA.

D.1. Cumulative Hazard Assessment: Relative Potency Estimation for Flumethrin

The 2011 pyrethroid CRA relies on the relative potency factor (RPF) approach using administered dose as the metric for quantifying chemical potency. In the RPF approach, the toxic potency of each chemical in the common assessment group (CAG) is determined. One member of the CAG is selected as the index chemical which is used as the point of reference for standardizing neurobehavioral potency of the other members of the CAG. In order to develop such potency estimates, EPA prefers to use a uniform measure of toxicity. In other words, the Agency prefers to use data which are from the same endpoint and same duration and to the extent possible any other factors which effect potency (e.g., time to peak effect, sex, etc).

In the pyrethroid CRA, the Agency used the two special WIL Functional Observational Battery (FOB) studies for estimating relative potency. This data was selected because these studies examined many behaviors, including key ones for evaluating neurotoxicity specific to pyrethroids. Specifically, the studies looked at a number of key parameters that are directly relevant to the Type I (e.g., hyperthermia tremors and clonus) and Type II (e.g., hypothermia, salivation, and mobility) syndromes. In addition to the WIL FOB studies, there is another study (Wolansky et al, 2006) which provides a high quality data set for estimating relative potency. Whereas the WIL FOB studies focus on endpoints specific to pyrethroid toxicity syndromes, the Wolansky study measured motor activity. Motor activity is considered an apical endpoint because it measures alterations in the activity level of an intact rat. Although the Wolansky study provides a potential data source for a uniform measure of potency, it was not utilized in the

CRA because of the lack of specific relevance to the common mechanism of action for the pyrethroids.

Although the existing toxicology database for assessment of flumethrin as a single chemical is complete with respect to the requirements for a non-food use pesticide; a specially designed FOB study is not currently available for flumethrin for use in estimating an RPF for use in the pyrethroid CRA. Flumethrin was also not one of the pyrethroids included in the Wolansky study. In lieu of this data, the Agency used the flumethrin acute neurotoxicity (ACN) study to estimate an RPF for flumethrin. In the flumethrin ACN study, effects consistent with pyrethroid toxicity syndromes (salivation and staining) are only observed at high doses and thus lack good dose response data. In contrast, motor activity shows a dose response relationship. As such, the Agency has elected to estimate the RPF for flumethrin using this motor activity data instead of the salivation data. This is not the preferred approach to estimating relative potency as motor activity does not represent the same measure of toxicity used for the other pyrethroids.

In order to estimate an RPF for flumethrin, the Agency is using the BMD for deltamethrin (i.e., the index chemical for the pyrethroids) from the Wolansky study compared with the POD from the flumethrin motor activity data. Using the deltamethrin motor activity data as the basis for estimating relative potency is preferred over the deltamethrin data from the WIL FOB as it is more appropriate to compare similar toxic effects. In other words, it is more appropriate to compare motor activity data to motor activity data than a comparison of motor activity data to FOB data. The relative potency estimates between the Wolansky and WIL FOB studies are remarkably similar (Table D.1). For the pyrethroids that have data from both studies, 8 of 11 RPFs differ by 2-fold or less.

In summary, developing an RPF in this manner is not expected to underestimate the contribution of flumethrin to the CRA as the RPFs developed using FOB data are very similar to the RPFs developed using the motor activity data for each pyrethroid. Flumethrin would be expected to have a similar RPF to the one calculated using motor activity data if a flumethrin FOB study was available. However, the Agency would prefer to use special FOB data in the relative potency determination for flumethrin . As noted in Section 2.1, the Agency encourages the development of special FOB data for flumethrin as this data would reduce the uncertainty associated with this approach.

Appendix Table D.1: Pyrethroid RPF Comparison FOB vs. Motor Activity		
Pyrethroid	FOB	Motor Activity
lambda-cyhalothrin	1.63	2.7 [a]
tefluthrin	1.36	0.68 [a]
cyfluthrin	1.15	1.75 [a]
bifenthrin	1.01	0.60 [a]
deltamethrin	1.00	1.00 [a]
fenpropathrin	0.50	0.38 [a]
metofluthrin	0.48	--
esfenvalerate	0.36	2.09 [a]
cypermethrin	0.19	0.23 [a]
tau-fluvalinate	1.00	--
cyphenothrin	0.15	--
d-allethrin	0.11	--
allethrin	0.11	0.03 [a]
prallethrin	0.10	--
permethrin	0.09	0.040 [a]
resmethrin	0.05	0.02 [a]
pyrethrins	0.02	--
imiprothrin	0.02	--
flumethrin	--	5.02 [b]

a Represents motor activity data from the Wolansky study
b Represents motor activity data from the flumethrin ACN study

D.2. Cumulative Exposure and Risk Issues

No pyrethroid pet collars were included in the 2011 pyrethroid CRA as there were no registered pet collars that contain pyrethroids at that time. The CRA did include a number of other pyrethroid pet products (e.g., spot-on, aerosol, shampoo, and trigger pump sprayer formulations). In order to determine if the proposed flumethrin pet collar will significantly contribute to or change the overall findings in the pyrethroid CRA the Agency performed a quantitative exposure and risk assessment. This assessment used the flumethrin RPF discussed above in Section D.1 as well as the same exposure algorithms and inputs that were used in the 2011 pyrethroid CRA.

The MOEs calculated and presented in Appendix Table D.2 were compared with the MOEs currently driving pet exposure and risk estimates in Table 6.4.7a from the 2011 pyrethroid CRA. Dermal adult pet handler exposure and risk estimates are currently driven by the permethrin pet shampoo use pattern with a dermal MOE of 27,000 which is lower than the estimated MOE for flumethrin (190,000). Dermal adult and 1 < 2 year old pet post-application exposure and risk estimates are currently driven by the cyphenothrin spot-on use pattern with adult and 1 < 2 year old dermal MOEs of 9,800 and 4,200, respectively, both of which are lower than the estimated MOEs for flumethrin (33,000 and 14,000, respectively). For 1 < 2 year olds, hand-to-mouth pet post-application exposure and risk estimates are currently driven by the cyphenothrin spot-on use pattern with an MOE of 22,000, which is lower than the estimated MOE for flumethrin (72,000). A summary of these MOEs is presented in Appendix Table D.2 while the detailed calculations are presented in Appendix Table D.3. In all cases, the estimated flumethrin MOEs using the RPF method were higher (i.e., less of a risk concern) than those used in the 2011 pyrethroid CRA. Thus the Agency has determined that the proposed flumethrin pet collar use will not significantly contribute to or change the overall findings in the 2011 pyrethroid CRA.

Appendix Table D.2: Comparison of Flumethrin MOEs with Pyrethroid Cumulative MOEs

Chemical		Scenario	Route	Population	MOE
New Use	Flumethrin	Pet collar	Handler dermal	Adult	190,000
			Postapp dermal	Adult	33,000
				Children (1 < 2 yr old)	14,000
			Postapp Hand-to-Mouth	Children (1 < 2 yr old)	72,000
CRA	Permethrin	Pet shampoo	Handler dermal	Adult	27,000
	Cyphenothrin	Pet spot-on	Postapp dermal	Adult	9,800
				Children (1 < 2 yr old)	4,200
			Postapp Hand-to-Mouth	Children (1 < 2 yr old)	22,000

Appendix Table D.3: Flumethrin Screening Level "Cumulative" MOEs

Pet Handler Exposure

Exposure Scenario	Application Rate (mg ai/dog)	Amount Treated Daily (animals)	Baseline Dermal Unit Exposure (mg/lb ai)	Baseline Inhalation Unit Exposure (mg/lb ai)	Baseline Dermal Unit Exposure (mg/lb ai)	Baseline Inhalation Unit Exposure (mg/lb ai)	Baseline Dermal Dose	Adjusted Baseline Dermal Dose (mg/kg/day) [a]	Adjusted Baseline Dermal MOE [b]	Baseline Inhalation Dose	Adjusted Baseline Inhalation Dose (mg/kg/day)	Baseline Inhalation MOE
Pet Dermal (adults)	16.7	2	220	NA	220	N/A [b]	0.0000113	0.000057	190,000	N/A [b]		

Pet Post-application Hand-to-Mouth Exposure

Exposure Scenario	Fai_{hands}	1-2 yr old Dermal Exposure	SA_H (cm2)	HR_t (mg/cm2)	F_M Fraction of Hand Surface Area Mouthed / Event	Exposure Time (hours/day)	N_Replen Number of replenishment intervals per hr (intervals/hr)	SE Extraction by Saliva	Freq_HtM H-t-M events per hour	BW	Average Daily Dose (mg/kg/day)	Adjusted Dose (mg/kg/day) [a]	Adjusted MOE [b]
Hand to Mouth (1 < 2 year olds)	0.039	0.03401	150	4.4214E-06	0.13	0.99	4	0.5	20	11.4	0.0000290	0.000145646	72,000

Pet Post-application Dermal Exposure

Exposure Scenario	Application Rate (mg ai/dog)	Body Weight (kg)	Fraction of App Rate Available	Surface Area of Medium Dog (cm2/animal)	Transferable Residue	Transfer Coefficient (cm2/hr)	Exposure Time (hours)	Absorbed Dermal Dose (mg/kg/day)	Adjusted Dose (mg/kg/day) [a]	Adjusted MOE [b]
Pet Dermal (1 < 2 year olds)	16.7	11.4	0.00960	7000	0.00002	1,500	0.99	0.00014917	0.00074883	14,000
Pet Dermal (adults)	16.7	71.8	0.00960	7000	0.00002	5,200	0.77	6.38601E-05	0.00032058	33,000

a Doses were adjusted based on an estimated flumethrin RPF of 5.02
b MOEs were calculated by comparing the adjusted dose to the oral BMD_{20} from the WIL FOB data for the index chemical, deltamethrin (14.5 mg/kg/day)
c Handler inhalation exposure is expected to be negligible from flumethrin pet collars and thus a quantitative assessment was not performed.

ED_005739A_00099209-00050

Message

From: Adler, Bonnie [Adler.Bonnie@epa.gov]
Sent: 8/23/2016 11:31:31 AM
To: Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]
Subject: Seresto - Human Exposure Analysis document
Attachments: Human Case Assessment Critique 2016_08_19.pdf

Sensitivity: Company Confidential

Confidential info sent by Bayer for Seresto [flumethrin]

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Friday, August 19, 2016 4:10 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>; Adler, Bonnie <Adler.Bonnie@epa.gov>; Bruce Martin <bruce.martin@bayer.com>
Subject: Seresto - Human Exposure Analysis document

Dear Mr. Davis,

Bayer became aware at the meeting with the Agency on 17 Aug 2016 that EPA is in the final stage of conducting a safety review of pyrethroids, including Flumethrin (one of the active ingredients in Seresto pet collar), and were invited to submit any relevant information until end of this week.

Ex. 4 CBI - Potential claims

Please forward this CONFIDENTIAL information to the appropriate Agency staff as soon as possible, for their immediate use and consideration.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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Docket Number EPA-HQ-OPP-2016-0031
www.regulations.gov

Flumethrin Preliminary Work Plan

Registration Review: Initial Docket

Case Number 7456

September 2016

Approved by: _____
Yu-Ting Guilaran
Director
Pesticide Re-evaluation Division

Date: _____

Flumethrin Preliminary Work Plan – Table of Contents

[TOC \o "1-3" \h \z \u]

References:

This Preliminary Work Plan summarizes the Environmental Protection Agency's current position based on the following documents:

1. *Flumethrin. Preliminary Problem Formulation and Ecological Risk Assessment and Effects Determination in Support of Registration Review.* I. Negrón-Encarnación. July 5, 2016

2. *Flumethrin. Human Health Assessment Scoping Document in Support of Registration Review* Julie Van Alstine, Monica Hawkins, Evisabel Craig, Wade Britton. September 7, 2016.

3. *Flumethrin: Tier I Review of Human Incidents and Epidemiology for Draft Risk Assessment.* Shanna Recore, Elizabeth Evans. September 7, 2016

These and other supporting documents for the flumethrin registration review case may be found in the docket EPA-HQ-OPP-2016-0031 at [HYPERLINK "http://www.regulations.gov"].

OVERVIEW

The docket for flumethrin is now open, initiating the first public comment period for this registration review (docket number EPA-HQ-OPP-2016-0031. Flumethrin (*RS*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-(*EZ*)-3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate (CAS No. 69770-45-2), is a Type II synthetic pyrethroid insecticide. Flumethrin is registered as a technical grade active ingredient (TGAI) and in one end-use product (EP) for use as a pet collar, which also includes the neonicotinoid insecticide imidacloprid (CAS 138261-41-3; PC Code 129099). It is used for the prevention and treatment of ticks, fleas, and lice on dogs and cats. The collars are to be left on the pet for up to 8 months. Flumethrin has no registered food or agricultural uses and is used primarily in residential areas.

This Preliminary Work Plan (PWP) document explains what EPA's Office of Pesticide Programs knows about flumethrin, highlighting anticipated data and assessment needs, identifying the types of information that would be especially useful to the Agency in conducting the review, and providing an anticipated timeline for completing the registration review for flumethrin. This PWP also includes a summary of the draft ecological risk assessment for flumethrin registration review. Both the ecological risk assessment and this PWP are now available in the docket and the 60-day comment period has commenced

The registration review process was designed to include a public participation component to solicit input from interested stakeholders. The Agency intends, by sharing this information in the docket, to inform the public of what it knows about flumethrin and what types of new data or other information would be helpful for the Agency to receive as it moves toward a decision on flumethrin. The Agency encourages all interested stakeholders to review the PWP and Appendix and to provide comments and additional information that will help the Agency's decision-making process for this chemical. In addition to general areas on which persons may wish to comment, there are some areas identified in the PWP and Appendix about which the Agency specifically seeks comments and information. Interested stakeholders could include: environmental non-profit or interest groups; pesticide manufacturers; commercial, institutional, residential, and other users of pesticides; or the public at large.

The Preliminary Work Plan begins by listing the anticipated data needs for flumethrin. Next, it discusses the statutory and regulatory authority for Registration Review. Then the document provides chemical facts, use and usage information, recent actions, the anticipated risk assessments, and a projected registration review timeline for flumethrin. Finally, the Appendix to this document includes identification and discussion of some areas that are considered generally in Registration Review along with some additional chemical case-specific information.

ANTICIPATED DATA NEEDS

Table 1 below summarizes anticipated data needs for flumethrin. For additional discussion of the anticipated data needs, see the *Flumethrin. Human Health Assessment and Scoping Document in Support of Registration Review.*

Table 1: Anticipated Data Needs for the Flumethrin Registration Review

Guideline Number	Study Title	Test Material[1]	Estimated Timeframe (Months from receipt of DCI)
Anticipated Data Needs for Flumethrin			
	Pet Transferrable Residue Study[2]	TEP	24

[1]TEP = typical end-use product
[2]Since the test material is co-formulated with Imidacloprid, both active ingredients must be tested.

STATUTORY AND REGULATORY AUTHORITY

The Food Quality Protection Act (FQPA) of 1996 mandated a registration review program. All pesticides distributed or sold in the United States (U.S.) generally must be registered by the Environmental Protection Agency (EPA or the Agency), based on scientific data showing that they will not cause unreasonable risks to human health or the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects to human health or the environment. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided on EPA's website.[1]

The Agency is implementing the registration review program pursuant to Section 3(g) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The regulations governing registration review begin at 40 CFR 155.40. The Agency will consider benefits information and data as required by FIFRA. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision. After reviewing and responding to comments and data received in the docket during this initial comment period, the Agency will develop a Final Work Plan (FWP) and anticipated schedule for the registration review of flumethrin.

[3] http://www.epa.gov/oppsrrd1/registration_review/

CHEMICAL FACTS

Table 2 provides a summary of the chemical facts for flumethrin.

Table 2: Chemical Facts for Flumethrin	
PC code	036007
Case Number	7456
CAS Number	69770-45-2
Year first registered	2012
Pesticide Type	Insecticide
Chemical class	Type II Synthetic Pyrethroid
Reregistration Eligibility Decision (RED)	Registered after November 1984, and was not subject to reregistration.
Tolerance Reassessment Eligibility Decision (TRED)	Not applicable. No Reregistration Eligibility Decision (RED) was developed for this case.
Cumulative group	The Agency has determined that based on its chemical structure and based on the observation of neurobehavioral effects consistent with Type II pyrethroids, flumethrin should be included in the common mechanism grouping (CMG) for this class of pesticides.
40 CFR Citation	There are no established or proposed tolerances for flumethrin in or on any food or feed crops.
Dual-use	Flumethrin is registered for conventional pesticidal uses only and has no registered antimicrobial or biopesticidal uses.
Non-pesticidal uses	There are no identified non-pesticidal uses of flumethrin.
Pesticide Re-evaluation Division, Chemical Review Manager	Maria Piansay [HYPERLINK "mailto:Piansay.maria@epa.gov"] (703)308-8063
Registration Division, Product Manager	Kable Davis [HYPERLINK "mailto:Davis.kable@epa.gov"] (703) 306-0415

USE AND USAGE INFORMATION

Table 3 summarizes the use and usage information for flumethrin.

Table 3: Flumethrin Use and Usage Information	
Summary of Use	Flumethrin is a Type II synthetic pyrethroid insecticide (Ectoparasiticide) for the control of ticks, fleas, lice, and mites (pet collars) for use in cat and dog collars that also contain the active ingredient imidacloprid.
Use Sites	Flumethrin is registered for use in residential and occupational applications. It is not currently registered for food or agricultural uses.
Summary of Usage	EPA has very limited usage data for flumethrin due to its non-agricultural and diffuse types of use patterns. Since it was registered in 2012, data were not available.
Formulation Type(s)	Impregnated plastic collar
Application Method(s)	Attached to pet around neck
Technical Registrant(s)	Bayer Healthcare LLC, Animal Health Division
No. of Registrations	2 Section 3 products- 1 technical and 1 end-product.[2]
Restricted Use	No

RECENT ACTIONS

Ex. 5 Deliberative Process (DP)

RISK ASSESSMENTS FOR REGISTRATION REVIEW

The most recent ecological and environmental fate risk assessment was completed on July 5, 2016, Findings and conclusions from these risk assessments are summarized in the *Flumethrin. Preliminary Problem Formulation and Ecological Risk Assessment and Effects Determination in Support of Registration Review.*

[2] Section 3 product labels can be obtained from the Pesticide Product Label System (PPLS) website (http://oaspub.epa.gov/pestlabl/ppls.home).

A. Ecological Risk Assessment

In preparation for this PWP, a combined problem formulation and preliminary ecological risk assessment and federally listed, threatened, and endangered species (also referred to as "listed" species) effects determination in support of the registration review of the insecticide flumethrin (PC Code 036007) was completed on July 5, 2016.

Flumethin is registered for use a pet collar which is affixed to a domesticated dog or cat. The labeled use and application method of flumethrin limit direct or indirect exposure to outdoor terrestrial areas given that the majority of animals treated primarily reside indoors. While there is potential for exposure to flumethrin vapors due to sublimation from the pet collar, the exposure is expected to be minimal and that the volatilized fraction is expected to dissipate rapidly through dilution with large volumes of air. In addition, the pet collar use of flumethrin is unlikely to result in exposure to aquatic resources or groundwater as any solubilized material will be diluted as well. Because of the low potential for non-target species to be exposed, only limited data have been submitted for this chemical. There are currently no toxicity data to assess the potential risk to other terrestrial or aquatic organisms from the registered use of flumethrin; however, risks to non-target organisms are not expected due to the low exposure potential.

Threatened/Endangered Species

Because of the predominantly indoor use of the product and low likelihood of exposure for terrestrial and aquatic organisms, there is no reasonable expectation of effects to listed species from the use of the currently registered flumethrin product. Therefore, EPA concludes that the currently registered use of flumethrin in pet collars is not expected to cause direct or indirect effects to federally-listed threatened and endangered species. A *No Effect* (NE) determination is made for all listed species, as well as a *No Habitat Modification* determination for all designated critical habitats for the currently registered use of flumethrin.

Endocrine Disruptor Screening Program

As part of its reregistration decision for flumethrin, EPA reviewed available data; however, since the likelihood of exposure to flumethrin is low, toxicity data for the compound have not been submitted. As required by FFDCA section 408(p) though, flumethrin is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[3]

B. Anticipated Human Health Risk Assessment

The most recent comprehensive human health assessment for flumethrin was completed on March 6, 2012 when flumethrin was initially registered in EPA. Findings and conclusions from

[3] [HYPERLINK "http://www.epa.gov/endo/"]

the assessment are summarized in *Flumethrin. Human Health Assessment Scoping Document in Support of Registration Review.*

During registration review, the Agency anticipates the need to conduct a revised residential post-application risk assessment. If toxicological endpoints or points of departure are revised based on the data that are anticipated to be required for registration review, they will be considered in the new assessments, as well as any changes to the standard operating procedures or default exposure assumptions.

Table 4 below summarizes the anticipated registration review risk assessments based on the HED Scoping Document.

Table 4: Anticipated Risk Assessments for the Flumethrin Registration Review		
Type of Risk Assessment	**Conduct?**	**Notes**
Ecological and Environmental Fate		
Comprehensive ecological (species to be assessed include terrestrial and aquatic organisms) including endangered species	N	The Agency has determined that the use of flumethrin is considered to be primarily a use with *de minimus* exposure for non-target organisms. A *No Effect* (NE) determination is made for all listed species, as well as a *No Habitat Modification* determination for all designated critical habitats. Therefore, an ecological risk assessment will not be conducted.
Incidents	N	There are no ecological risks to flumethrin since it is only for use as a pet collar, therefore, no ecological incidents are anticipated.
Human Health		
Dietary		
Food and Drinking water	N	A dietary (food and drinking water) exposure assessment is not required since there are no proposed or currently registered food uses for flumethrin and drinking water exposure is not expected from the registered uses.
Occupational		
Handlers (mixers, loaders, applicators)	N	A new occupational handler risk assessment is not anticipated to be needed during registration review.
Post-application	N	A new occupational post-application assessment is not anticipated to be needed during registration review.
Residential		
Handlers	Ex. 5 Deliberative Process (DP)	
Post-application		
Other		
Aggregate	N	There are currently no registered food uses for flumethrin and drinking water exposures are not expected from the registered pet collar uses of flumethrin; therefore, a quantitative aggregate risk assessment is not required at this time.
Cumulative	N	The Agency has performed a quantitative analysis of flumethrin, as part of the 2012 assessment for the flumethrin pet collar uses, and determined that the proposed flumethrin pet collar use will not significantly contribute to or change the overall findings in the pyrethroid cumulative risk assessment.

Tolerances	N	There are no established or proposed tolerances for flumethrin since it is not registered for use in or on any food or feed crops.
Incidents	Ex. 5 Deliberative Process (DP)	For a discussion of reported human incidents for flumethrin, see page 9 of the Scoping Document and the *Flumethrin: Tier I Review of Human Incidents and Epidemiology for Draft Risk Assessment.*

Ex. 5 Deliberative Process (DP)

Guidance for Commenters: Additional *human health information* requested for this registration review, and of particular interest to EPA, is described below.

- The Agency is seeking information on the relative amounts of solids (e.g., dust) or liquids available for exposure as a result of the use of flumethrin-impregnated pet collars. Without specific information or data, the Agency is unable to determine whether the end-use product should be assessed as a liquid, dust, or some combination of the two.
- The Agency is requesting additional information to inform the risk assessment for post-application residential exposure.

TIMELINE

EPA has created the following estimated timeline for the completion of the flumethrin registration review in Table 5 below.

Table 5: Projected Flumethrin Registration Review Timeline

Activities	Estimated Date
Opening the Docket	
Open Docket and 60-day Public Comment Period[2]	2016 - September
Close Public Comment	2016 - November
Case Development	
Final Work Plan	2017 – March
Issue DCI	2017 – April – June
Data Submission	2019 – April – June
60-day Public Comment Period for Draft Risk Assessments[1]	2020 – October - December
Registration Review Decision	
60-day Public Comment Period for Proposed Registration Review Decision	2021 – July - September
Registration Review Decision and Begin Post-Decision Follow-up	2022
Total (years)	6

[1] The regulations governing Registration Review generally require the Agency to provide a public comment period of at least 30 calendar days for draft risk assessments; see 40 CFR Part 155.53(c). For conventional pesticides, the Agency plans to provide a 60 calendar day public comment period generally for draft risk assessments.

[2] The Agency is seeking comment on the PWP and the ecological risk assessment during this comment period.

NEXT STEPS

After the 60-day public comment period closes, the Agency will review and respond to any comments received in a timely manner and then issue a Final Work Plan for the registration review of flumethrin.

Appendix – Additional Areas Considered in the Flumethrin Registration Review

PUBLIC COMMENTS AND FEEDBACK:

Guidance for Commenters: The areas below highlight topics of special interest to the Agency where your comments, data submissions, or reference to sources of additional information could be of particular use.

Ex. 5 Deliberative Process (DP)

Environmental Justice:

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To help address potential environmental justice issues, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to flumethrin compared to the general population. **Please**

Ex. 5 Deliberative Process (DP)

comment if you are aware of any sub-populations that may have atypical, unusually high exposure compared to the general population.

ENDOCRINE DISRUPTOR SCREENING PROGRAM:

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for flumethrin, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), flumethrin is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[8] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[9]

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[8] See [HYPERLINK "http://www.regulations.gov/" \l "!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074"] for the final second list of flumethrins.

[9] http://www.epa.gov/endo/

HUMAN STUDIES:

Residential

Past flumethrin risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal exposure; particularly data included in the Pet SOP from the 2012 Residential SOPs. EPA has reviewed all the studies supporting the SOPs and found no clear and convincing evidence that the conduct of any of them was either fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted. All applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied, and there is no regulatory barrier to continued reliance on these studies.

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 9/16/2016 11:11:31 AM
To: Goodis, Michael [Goodis.Michael@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
CC: Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Knorr, Michele [knorr.michele@epa.gov]
Subject: Seresto Briefing Document
Attachments: Seresto Briefing Document.docx

Everyone –

Please find attached the briefing document for next Tuesday's meeting with Jack regarding Seresto. Let me know if you have any questions.

Enjoy the day.
Bo

EPA-internal, confidential, deliberative

Seresto Briefing Document

Product Description

- Seresto is a dog and cat collar, which is intended to control fleas and ticks for up to 8 months.
- The collar contains 4.5% flumethrin and 10.0% imidacloprid. This is the only use for flumethrin.

Timeline

- **July 27, 2015:** EPA received a press inquiry alerting us to an alleged high number of reported pet incidents.
- **August 5, 2015:** Bayer submitted sales information for Seresto.
- **August 28, 2015:** Bayer submitted incident data using template suggested by EPA.
- **December 16, 2015:** RD and HED briefed upper management on the status of review for the incident data.
- **July 18, 2016:** OPP received the incident report outlining the overall findings and conclusions of PMRA's Seresto collar review.
- **August 10, 2016:** OPP was informed, via conference call, that PMRA would not register Seresto in Canada. As a result, Bayer withdrew the submission and requested PMRA not share any further documents with EPA.
- **September 1, 2016:** OPP completes its draft review of the incident data and PMRA's causality analysis. The document has not been finalized.
- **September 2, 2016:** EPA receives Bayer's critique of PMRA's Animal Incident Assessment. The document is in the process of being reviewed.
- **September 22, 2016:** Bayer has requested a meeting with EPA to discuss the scope of the flumethrin report that is to be made public by the end of September for Registration Review.

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Note – OGC is attending to address any legal concerns.

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 9/14/2016 1:01:07 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: Seresto Briefing Document
Attachments: Seresto Briefing Document.docx

Hi Marietta –

Here is the draft briefing document for next week's meeting with Jack. Let me know if you want anything revised. Also, I was questioning how I formatted the "Options for Next Steps" section. Let me know if you were envisioning something different.

Hope your trip is going well.
Bo

Seresto Briefing Document

Product Description

- Seresto is a dog and cat collar, which is intended to control fleas and ticks for up to 8 months.
- The collar contains 4.5% flumethrin and 10.0% imidacloprid. This is the only use for flumethrin.

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Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Appointment

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 9/12/2016 5:29:59 PM
To: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]

Subject: Bayer (Seresto) Pre-Meeting
Location: DCRoomPYS7621B/Potomac-Yard-One

Start: 9/12/2016 6:30:00 PM
End: 9/12/2016 7:00:00 PM
Show Time As: Tentative

Required Attendees: Guilaran, Yu-Ting; Vogel, Dana; Dan Rosenblatt; Arrington, Linda; Biscoe, Melanie; Piansay, Maria; Echeverria, Marietta

Let's meet and prepare for the upcoming meeting with Bayer regarding flumethrin (Seresto).

Call-in No:
Conf. Code

Ex. 6 PP - conference code/call in number

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 9/9/2016 1:12:48 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: RE: Heads up

Will do. Have a great weekend.

From: Echeverria, Marietta
Sent: Friday, September 09, 2016 9:07 AM
To: Davis, Kable <Davis.Kable@epa.gov>
Subject: Re: Heads up

Yes, thanks

Sent from my iPhone

On Sep 9, 2016, at 8:27 AM, Davis, Kable <Davis.Kable@epa.gov> wrote:

> I didn't invite you to the pre-meeting on Monday, since you can't attend the actual meeting with Bayer. Did you want me to send you an invite anyway?
>
> ---
>
> **From:** Davis, Kable
> **Sent:** Friday, September 09, 2016 8:01 AM
> **To:** Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Goodis, Michael <Goodis.Michael@epa.gov>; Vogel, Dana <Vogel.Dana@epa.gov>
> **Cc:** Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Arrington, Linda <Arrington.Linda@epa.gov>
> **Subject:** RE: Heads up
>
> Everyone –
>
> I scheduled the pre-meeting for Monday at 2:30 pm.
>
> Have a nice weekend.
> Bo
>
> ---
>
> **From:** Guilaran, Yu-Ting
> **Sent:** Friday, September 09, 2016 7:44 AM
> **To:** Goodis, Michael <Goodis.Michael@epa.gov>; Vogel, Dana <Vogel.Dana@epa.gov>
> **Cc:** Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Arrington, Linda <Arrington.Linda@epa.gov>
> **Subject:** RE: Heads up
>
> Sounds good. Can RD set up the pre-meeting? Thanks.
>
> Regards,
>
> Yu-Ting Guilaran, P.E.
> Director

Pesticide Re-evaluation Division (PRD)
Office of Pesticide Programs
Office of Chemical Safety and Pollution Prevention
(tel) 703 308 0052
(fax)703 308 8005
Mail code 7508P
Room number PY S9623

From: Goodis, Michael
Sent: Thursday, September 08, 2016 5:25 PM
To: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Vogel, Dana <Vogel.Dana@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>
Subject: FW: Heads up

Yu-Ting and Dana

I understand that Bayer is wanting to come in next week to meet with both of you to discuss flumethrin - Seresto pet collar concerns. I think RD should be there as well in light of our discussions with them on pet incident reporting, if that is agreeable.
Both Marietta and I will be out next week, but Bo and Dan R. can attend for RD to be part of the discussion. Also, I think it would be helpful to have a pre-meeting so that we are all clear on who/what will be said. What do you think?

Michael L. Goodis, P.E.
Acting Director, Registration Division (RD)
Office of Pesticide Programs (OPP)

Phone 703-308-8157
Room S7624

From: Echeverria, Marietta
Sent: Wednesday, September 07, 2016 6:06 PM
To: Goodis, Michael <Goodis.Michael@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Vogel, Dana <Vogel.Dana@epa.gov>
Cc: Arrington, Linda <Arrington.Linda@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>
Subject: Fwd: Heads up

FYI

Sent from my iPhone

Begin forwarded message:

> **From:** Bruce Martin <bruce.martin@bayer.com>
> **Date:** September 7, 2016 at 5:33:00 PM EDT
> **To:** "Davis, Kable" <Davis.Kable@epa.gov>, "Echeverria, Marietta" <Echeverria.Marietta@epa.gov>
> **Cc:** Doug Spilker <doug.spilker@bayer.com>, Bruce Martin <bruce.martin@bayer.com>
> **Subject: Heads up**
>
> Bo and Marietta,

This is an advanced notice that Bayer's upper management and legal departments are contacting Ms. Yu-Ting Guilaran and Dr. Dana Vogel to request an audience at EPA the week of September 12. The request is to meet in accordance with the stakeholder engagement provisions of 40 CFR to understand the scope of the flumethrin report that is to be made public by the end of September. If you have questions please let me know.

Best regards,

Bruce Martin
Director, Regulatory Affairs
Animal Health Development, North America

Bayer: Science for A Better Life

Bayer Animal Health
Bayer HealthCare LLC
12809 Shawnee Mission Pkwy
Shawnee, KS 66216
USA

Tel: +1 913 268 2779
Fax: +1 913 268 2075
Mobile: +1 913 5235048
E-mail: bruce.martin@bayer.com
Web: http://www.bayer.com

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Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 9/8/2016 1:41:24 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: RE: Additional Information - Critique of PMRA's Assessment for the Seresto Collar

Will do. Thanks.

From: Echeverria, Marietta
Sent: Thursday, September 08, 2016 9:41 AM
To: Davis, Kable <Davis.Kable@epa.gov>
Subject: RE: Additional Information - Critique of PMRA's Assessment for the Seresto Collar

No, please forward. Thanks. I know Colleen is looking at it.

From: Davis, Kable
Sent: Thursday, September 08, 2016 9:40 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: FW: Additional Information - Critique of PMRA's Assessment for the Seresto Collar

Hi Marietta –

Did you send this around to everyone while I was away?

Thanks,
Bo

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Friday, September 02, 2016 3:31 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Bruce Martin <bruce.martin@bayer.com>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>; Piansay, Maria <Piansay.Maria@epa.gov>
Subject: Additional Information - Critique of PMRA's Assessment for the Seresto Collar

Dear Mr. Davis,

Bayer became aware at the meeting with the Agency on 17 Aug 2016 that EPA is in the final stage of conducting a safety review of pyrethroids, including Flumethrin (one of the active ingredients in Seresto pet collar), and were invited to submit any relevant information.

Ex. 4 CBI - Potential Claims

Please forward this CONFIDENTIAL information to the appropriate Agency staff as soon as possible, for their immediate use and consideration.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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Message

From: Doug Spilker [doug.spilker@bayer.com]
Sent: 9/2/2016 7:30:43 PM
To: Davis, Kable [Davis.Kable@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Bruce Martin [bruce.martin@bayer.com]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]
Subject: Additional Information - Critique of PMRA's Assessment for the Seresto Collar
Attachments: Seresto Animal Assessment Bayer 2016_09_02 final.pdf

Dear Mr. Davis,

Bayer became aware at the meeting with the Agency on 17 Aug 2016 that EPA is in the final stage of conducting a safety review of pyrethroids, including Flumethrin (one of the active ingredients in Seresto pet collar), and were invited to submit any relevant information.

Ex. 4 CBI - Potential CBI

Please forward this CONFIDENTIAL information to the appropriate Agency staff as soon as possible, for their immediate use and consideration.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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Message

From: Davis, Donna [Davis.Donna@epa.gov]
Sent: 4/21/2016 7:29:01 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Breeden, Julie [Breeden.Julie@epa.gov]
CC: Evans, Elizabeth [Evans.Elizabeth@epa.gov]; Crowley, Matthew [Crowley.Matthew@epa.gov]; Adler, Bonnie [Adler.Bonnie@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Craig, Evisabel [Craig.Evisabel@epa.gov]; Hawkins, Monica [Hawkins.Monica@epa.gov]
Subject: RE: PMRA Seresto update from conference call today

Marietta and company,
Below is a summary from Evisabel Craig about the endpoint – let us know if you need anything more:

Ex. 5 Deliberative Process (DP)

From: Echeverria, Marietta
Sent: Thursday, April 21, 2016 1:55 PM
To: Recore, Shanna <Recore.Shanna@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden, Julie <Breeden.Julie@epa.gov>
Cc: Evans, Elizabeth <Evans.Elizabeth@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>; Adler, Bonnie <Adler.Bonnie@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Arrington, Linda <Arrington.Linda@epa.gov>
Subject: RE: PMRA Seresto update from conference call today

David et al.,
I spoke with Donna Davis this morning. She is having her team write up a brief technical summary (1-2 paragraphs) describing the endpoints. She feels pretty comfortable that our team is confident with our tox endpoint because they have looked at it for reg review. There is an outstanding question about **Ex. 5 Deliberative Process (DP)** **Ex. 5 Deliberative Process (DP)** PRD is hosting a call with Bayer tomorrow on this issue.

Shanna, Did PMRA say when they could share the assessment?

Thanks,
Marietta

From: Recore, Shanna
Sent: Wednesday, April 20, 2016 8:53 PM
To: Miller, David <Miller.DavidJ@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden, Julie <Breeden.Julie@epa.gov>
Cc: Evans, Elizabeth <Evans.Elizabeth@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>
Subject: RE: PMRA Seresto update from conference call today

Vicky (from PMRA) also said that they will be in touch next week, after the second director meeting, to schedule a conference call regarding PMRA's decision. She said the meeting will be on Thursday but she is not sure if it will be morning or afternoon.

From: Miller, David
Sent: Wednesday, April 20, 2016 4:31 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden, Julie <Breeden.Julie@epa.gov>
Cc: Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>
Subject: FW: PMRA Seresto update from conference call today

Just FYI – see below

Also, I will be on travel beginning tomorrow through 01 May, back in office on 02 May. Matt C. is acting. I've asked folks here to see you later this week or early next about what you in RD to be done Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

David.

From: Recore, Shanna
Sent: Wednesday, April 20, 2016 2:55 PM
To: Miller, David <Miller.DavidJ@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: FW: PMRA Seresto update from conference call today

I had a voicemail from Vicky Godfrey from PMRA when I got back to my desk. She said that they had the directors meeting today and that the directors agreed that the collar should not be registered.

From: Recore, Shanna
Sent: Tuesday, April 19, 2016 12:55 PM
To: Miller, David <Miller.DavidJ@epa.gov>
Cc: Evans, Elizabeth <evans.elizabeth@epa.gov>
Subject: PMRA Seresto update from conference call today

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Follow-up action items:

Vicky from PRMA is going to call me tomorrow after the management meeting to give an update.

Ex. 5 Deliberative Process (DP) and arrange another conference call after a 2nd management meeting that they anticipate taking place next week.

Shanna Recore
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
(703) 308-9399

Message

From: Recore, Shanna [Recore.Shanna@epa.gov]
Sent: 4/21/2016 1:55:45 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: RE: PMRA Seresto update from conference call today
Attachments: 48240227.DER.DOCX; 48240228.DER.DOCX

Hi Marietta,
Just following up from our discussion on Tuesday and David's email yesterday. I just had a voice mail from Vicky from

Ex. 5 Deliberative Process (DP)

From: Miller, David
Sent: Wednesday, April 20, 2016 4:31 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden, Julie <Breeden.Julie@epa.gov>
Cc: Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>
Subject: FW: PMRA Seresto update from conference call today

Just FYI – see below

Also, I will be on travel beginning tomorrow through 01 May, back in office on 02 May. Matt C. is acting. I've asked folks here to see you later this week or early next Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

David.

From: Recore, Shanna
Sent: Wednesday, April 20, 2016 2:55 PM
To: Miller, David <Miller.DavidJ@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: FW: PMRA Seresto update from conference call today

I had a voicemail from Vicky Godfrey from PMRA when I got back to my desk. She said that they had the directors meeting today and that the directors agreed that the collar should not be registered.

From: Recore, Shanna
Sent: Tuesday, April 19, 2016 12:55 PM
To: Miller, David <Miller.DavidJ@epa.gov>
Cc: Evans, Elizabeth <evans.elizabeth@epa.gov>
Subject: PMRA Seresto update from conference call today

Ex. 5 Deliberative Process (DP)

Follow-up action items:

Vicky from PRMA is going to call me tomorrow after the management meeting to give an update.

Ex. 5 Deliberative Process (DP) and arrange another conference call after a 2nd management meeting that they anticipate taking place next week.

Shanna Recore
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
(703) 308-9399

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 8/4/2016 8:04:45 PM
To: Goodis, Michael [Goodis.Michael@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: FW: Pet Collars

Hi Mike –

Peter Brander is out of the office next week. Would you still like to be invited to the conference call with PMRA next week regarding Seresto?

Thanks much,
Bo

From: Echeverria, Marietta
Sent: Tuesday, August 02, 2016 9:12 AM
To: Goodis, Michael <Goodis.Michael@epa.gov>; Laws, Meredith <Laws.Meredith@epa.gov>
Cc: Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Lewis, Susan <Lewis.Susan@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>
Subject: RE: Pet Collars

Mike, we have a team meeting tomorrow. I can make a better recommendation about when to meet with PMRA (before or after the Bayer meeting) after that meeting. Thanks

---

From: Goodis, Michael
Sent: Monday, August 01, 2016 9:01 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Laws, Meredith <Laws.Meredith@epa.gov>
Cc: Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Lewis, Susan <Lewis.Susan@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>
Subject: RE: Pet Collars

Ex. 5 Deliberative Process (DP)

Maybe propose a meeting with PMRA later in August. I just need to get back with them on timing for now so let me know when would be a good day.

A separate briefing would be helpful. Feel free to set one up when ready...thanks

Michael L. Goodis, P.E.
Acting Deputy Director, Registration Division (RD)
Office of Pesticide Programs (OPP)

Phone 703-308-8157
Room S7624

From: Echeverria, Marietta
Sent: Monday, August 01, 2016 8:55 AM
To: Laws, Meredith <Laws.Meredith@epa.gov>; Goodis, Michael <Goodis.Michael@epa.gov>
Cc: Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Lewis, Susan <Lewis.Susan@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>
Subject: RE: Pet Collars

This is the Seresto collar (flumethrin/imidacloprid). We had a call with PMRA on 7/12. This product is registered here but pending registration at PMRA. Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP) Let me know if you'd like a briefing or if I can bring you up to speed during a general.

Thanks,
Marietta

From: Laws, Meredith
Sent: Friday, July 29, 2016 9:13 AM
To: Goodis, Michael <Goodis.Michael@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Lewis, Susan <Lewis.Susan@epa.gov>
Subject: RE: Pet Collars

Mike - I'm not sure exactly what the topic is about except t Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP) Marietta & I will chat when she gets back, maybe this has to do with a collar that I know her branch has had issues with.

Meredith

From: Goodis, Michael
Sent: Friday, July 29, 2016 9:05 AM
To: Laws, Meredith <Laws.Meredith@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Lewis, Susan <Lewis.Susan@epa.gov>
Subject: Pet Collars

Meredith and Marietta

Please see the note below from PMRA about setting up a time to discuss flumethrin/imidicloprid pet collars.
I believe imidacloprid is with Meredith and flumethrin is with Marietta. Can you fill me in on the topic to discuss and let me know whether we are ready to discuss with PMRA by mid-August?
I need to get back to them to set it up. Thanks

Michael L. Goodis, P.E.
Acting Deputy Director, Registration Division (RD)
Office of Pesticide Programs (OPP)

Phone 703-308-8157
Room S7624

From: Brander, Peter (HC/SC) [mailto:peter.brander@canada.ca]
Sent: Tuesday, July 26, 2016 4:42 PM
To: Goodis, Michael <Goodis.Michael@epa.gov>
Cc: Hart, Connie (HC/SC) <connie.hart@canada.ca>; Silva, Minoli (HC/SC) <minoli.silva@canada.ca>; O'Reilly, Joanna (HC/SC) <joanna.oreilly@canada.ca>; Sterkenburg, Neilda (HC/SC) <neilda.sterkenburg@canada.ca>; Lamarche, Natalie (HC/SC) <natalie.lamarche@canada.ca>
Subject: RE: Draft of the pyriofenone chronic bee study

Ex. 6 Personal Privacy (PP)

In my absence, should you agree that it would be of value to have our evaluators discuss the science further, I would ask that you contact Connie Hart, who I have copied on this email. Connie is aware of the file and would be able to assist in pulling together the HC particpants for such a discussion.

I was also wondering if we could look to book a meeting for mid-August as a follow-up to the recent discussion between PMRA and the EPA with regard to the review of flumethrin/imidicloprid pet collars. The PMRA had committed to a follow-up meeting with the EPA once we had met with Bayer on this file. I will look to have my EA book this meeting for mid August.

Thank you.

Peter J Brander

Chief Registrar and Director General, Pest Management Regulatory Agency
Health Canada / Government of Canada
peter.brander@canada.ca / Tel: 613-736-3704

Chef de l'homologation et Directeur général, Agence de réglementation de la lutte antiparasitaire
Sante Canada / Gouvernement du Canada
peter.brander@canada.ca / Tél : 613-736-3704

From: Goodis, Michael [mailto:Goodis.Michael@epa.gov]
Sent: 2016-07-25 12:11 PM
To: Brander, Peter (HC/SC)
Subject: RE: Draft of the pyriofenone chronic bee study

Hi Peter

Just letting you know that I got your voicemail and we are looking into it.
I will be in touch when we find out....

Michael L. Goodis, P.E.
Acting Deputy Director, Registration Division (RD)
Office of Pesticide Programs (OPP)

Phone 703-308-8157
Room S7624

From: Goodis, Michael
Sent: Tuesday, July 19, 2016 5:29 PM
To: 'Brander, Peter (HC/SC)' <peter.brander@canada.ca>
Cc: Lewis, Susan <Lewis.Susan@epa.gov>
Subject: FW: Draft of the pyriofenone chronic bee study

Hi Peter

Attached is the study review that we discussed. Let me know when you are ready to discuss again.

Michael L. Goodis, P.E.
Acting Deputy Director, Registration Division (RD)
Office of Pesticide Programs (OPP)

Phone 703-308-8157
Room S7624

From: McCall, Deborah
Sent: Tuesday, July 19, 2016 4:23 PM
To: Goodis, Michael <Goodis.Michael@epa.gov>
Subject: Draft of the pyriofenone chronic bee study

Attached is the draft copy of the pyriofenone chronic bee study.

Deborah McCall (Debbie)
Chief, Invertebrate & Vertebrate Branch 2
USEPA
Office of Pesticide Programs
1200 Pennsylvania Ave., NW (7505P)
Washington, DC 20460
703.605.0717
mccall.deborah @epa.gov

From: VA-PYS-7971-M@epa.gov [mailto:VA-PYS-7971-M@epa.gov]
Sent: Tuesday, July 19, 2016 4:25 PM
To: McCall, Deborah <McCall.Deborah@epa.gov>
Subject:

Message

From: Isbell, Diane [Isbell.Diane@epa.gov]
Sent: 6/28/2016 3:57:03 PM
To: Beaudoin, Josee (HC/SC) [josee.beaudoin@canada.ca]; Squires, Janice (HC/SC) [janice.squires@canada.ca]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Sterkenburg, Neilda (HC/SC) [neilda.sterkenburg@canada.ca]
Subject: FW: review of flumethrin/imidicloprid pet collar - request for a conference call

Hi Josee and Janice,
Susan Lewis and Marietta Echeverria are interested in having a conference call with Peter and Neilda on the review of incident data associated with the Bayer Seresto pet collar (combination of imidacloprid and flumethrin). It sounds like EPA's HED have been collaborating with PMRA on these reviews. EPA met with Bayer last week and it sounds like you might be meeting with them this week.

Please let me know if it is possible to have a conference call to discuss the reviews.

Thanks for your help with this!

Best regards,
Diane

÷÷÷÷÷÷÷÷÷÷÷÷÷÷÷÷÷÷÷÷÷÷÷÷
Diane Isbell
Special Assistant
Registration Division, 7505P
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460
703-308-8154

From: Echeverria, Marietta
Sent: Tuesday, June 28, 2016 9:04 AM
To: neilda.sterkenburg@canada.ca
Cc: Isbell, Diane <Isbell.Diane@epa.gov>
Subject: FW: review of flumethrin/imidicloprid pet collar

Hi Neilda,

I'm resending this in case you missed it. Susan Lewis is interested in having a conference call with you and Peter on this issue. I'm looping Diane Isbell in so she can help with scheduling. Is there anyone Diane should work with on this?

Thanks,
Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1
Registration Division
Office of Pesticide Programs
703-305-8578

http://www.epa.gov/pesticide-registration

From: Echeverria, Marietta
Sent: Tuesday, June 14, 2016 2:22 PM
To: 'neilda.sterkenburg@canada.ca' <neilda.sterkenburg@canada.ca>
Subject: review of flumethrin/imidicloprid pet collar

Greetings Neilda,

My name is Marietta Echeverria and I am a branch chief in the Registration Division of EPA's OPP. I met you when you were visiting a few months ago. Our reviewers in HED have been collaborating with your reviewers in HED on the review of incident data associated with the Bayer Seresto pet collar (combination of imidacloprid and flumethrin). We met with Bayer last week and I understand that you were meeting with them this week. Are you available for a phone call this week to discuss the status of the reviews?

Thanks,
Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1
Registration Division
Office of Pesticide Programs
703-305-8578
http://www.epa.gov/pesticide-registration

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 8/3/2016 10:51:33 AM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]
Subject: FW: Agenda 8/3/16 - Pyrethroid Team Meeting
Attachments: Agenda 8_3_16 pyrethroid team mtg.docx; Pyrethroid Registration Review Schedule Summary.docx

Hi Marietta and Julie –

Should one of us attend this pyrethroid meeting today? Unfortunately, we are all invited to the Seresto pre-meeting. Their suggested language looks fine to me, however I don't think Ex. 5 Deliberative Process (DP) Ex. 5 Deliberative Process (DP) Marietta – you had suggested the text should explain the Ex. 5 Deliberative Process (DP) I'm guessing they Ex. 5 Deliberative Process (DP) Ex. 5 Deliberative Process (DP)

Thanks,
Bo

From: Waleko, Garland
Sent: Tuesday, August 02, 2016 5:24 PM
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Subject: Agenda 8/3/16 - Pyrethroid Team Meeting

Agenda – Interdivisional Pyrethroid Team Meeting
8/3/16, 3:00-3:30 pm

HED

- Any updates or issues? The most recent schedule is attached.

RD

- Pet incident data - from our last discussion there were a few different suggestions on how to address pet incidents with pyrethroids. Please look over the text below to see if this level of information would be adequate or if we want to say anything else at this time.

  Draft Pet Incident Summary - There are a number of pyrethroids with registered use as direct treatment on pets. Some of the most popular pet products are spot-on products. EPA has been engaged with stakeholders on a variety of different actions to address risks to pets from the use of pet spot-on products; additional information on this project can be found here: https://www.epa.gov/pets/epa-evaluation-pet-spot-products-analysis-and-plans-reducing-harmful-effects. As additional information is gathered through this project EPA will be evaluating the use of pet spot-on products, including those that contain pyrethroids, to determine if additional changes are needed to those registrations. (Do we want to say anything about future plans to

Ex. 5 Deliberative Process (DP)

EFED/PRD

- **Agricultural and mosquito section** – in review in PRD
- **Rationale document** – draft with Mah for PRT review as far as general direction and conclusions. Draft is also with PRD management. PRD doesn't expect comments at this point, and will have an updated draft in the middle of August for more detailed review
- **Bee section**?
- Stakeholder meetings - PWG August meeting, PWG October benefits meeting, California wastewater/stormwater folks

BEAD

- Characterization for Agricultural section – holding off to finalize
- Mosquito section progress/issues?

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Agenda – Interdivisional Pyrethroid Team Meeting
8/3/16, 3:00-3:30 pm

HED

- Any updates or issues? The most recent schedule is attached.

RD

- Pet incident data - from our last discussion there were a few different suggestions on how to address pet incidents with pyrethroids. Please look over the text below to see if this level of information would be adequate or if we want to say anything else at this time:

  Pet Incident Summary - There are a number of pyrethroids with registered use as direct treatment on pets. Some of the most popular pet products are spot-on products. EPA has been engaged with stakeholders on a variety of different actions to address risks to pets from the use of pet spot-on products; additional information on this project can be found here: [HYPERLINK "https://www.epa.gov/pets/epa-evaluation-pet-spot-products-analysis-and-plans-reducing-harmful-effects"]. As additional information is gathered through this project EPA will be evaluating the use of pet spot-on products, including those that contain pyrethroids, to determine if additional changes are needed to those registrations. (Do we want to say anything about future Ex. 5 Deliberative Process (DP) s?)

EFED/PRD

- **Agricultural and mosquito section** – in review in PRD
- **Rationale document** – draft with Mah for PRT review as far as general direction and conclusions. Draft is also with PRD management. PRD doesn't expect comments at this point, and will have an updated draft in the middle of August for more detailed review
- **Bee section**?
- Stakeholder meetings - PWG August meeting, PWG October benefits meeting, California wastewater/stormwater folks

BEAD

- Characterization for Agricultural section – holding off to finalize
- Mosquito section progress/issues?

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 8/30/2016 12:39:36 PM
To: Overstreet, Anne [overstreet.anne@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: Seresto Documents
Attachments: HED Risk Assessment.pdf; Acute Toxicity Review.pdf; Companion Animal Review.pdf; Rate of Release Document.pdf

Hi Anne –

Here are the reviews used to originally register Seresto. I've included the following:

1. HED Risk Assessment
2. Acute Toxicity Review
3. Companion Animal Review
4. Rate of Release Document

Question – do you happen know if the tribes have been reporting these Seresto incidents? Also, do you have any idea on the number and severity?

Hope this helps.
Bo

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: March 6, 2012

SUBJECT: Flumethrin: Human Health Risk Assessment for the Section 3 Registration Action for Cat and Dog Collars

PC Code: 036007
Decision No.: 440305
Petition No.:
Risk Assessment Type: Single Chemical/Aggregate
TXR No.:
MRID No.: 48240139

DP Barcode: D392125
Registration No.:
Regulatory Action: Section 3 Registration
Case No.: None

CAS No.: 69770-45-2
40 CFR:

FROM: Charles Smith, Senior Environmental Scientist/Risk Assessor
Marquea King, Ph.D., Toxicologist
Risk Assessment Branch VI
Health Effects Division (7509P)

THROUGH: Felecia Fort, Chief
Risk Assessment Branch VI
Health Effects Division

and

P.V. Shah, Ph.D.
Margarita Collantes
Risk Assessment Review Committee
Health Effects Division

TO: BeWanda Alexander/Richard Gebken, Risk Management Team 10
Insecticide Branch
Registration Division (7505P)
Risk Management Division

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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. Bayer Healthcare LLC has requested registration of the new active ingredient (ai) flumethrin for use in cat and dog collars. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed pet collar uses of flumethrin.

HED has evaluated the toxicity and exposure databases for the new active ingredient, flumethrin, and has conducted a human health risk assessment in support of the proposed uses. Based on this assessment, HED has determined that there are no potential risk estimates of concern for the proposed uses of flumethrin. HED recommends that the requested uses be granted.

A summary of the findings and an assessment of human health risk resulting from the proposed uses for flumethrin are provided in this document. The HED team members contributing to this risk assessment include Marquea King (hazard evaluation) and Charles Smith (occupational/residential and risk assessment).

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1.0 Executive Summary

Bayer Healthcare LLC has requested registration of the new active ingredient (ai) flumethrin for use in cat and dog collars. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed pet collar uses of flumethrin. This document contains the human health exposure and risk assessment for the requested uses.

Use Profile: Flumethrin (*RS*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-(*EZ*)-3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate is a synthetic pyrethroid insecticide. Flumethrin is being proposed for use in cat and dog collars that also contain imidacloprid. There are two different sizes of collar being proposed both of which contain 4.5% flumethrin and 10% imidacloprid. The small collar weighs 12.5 grams and is intended for use on cats and small dogs up to 8 kg in weight. The large collar weighs 45 grams and is intended for use on dogs over 8 kg in weight.

Hazard Assessment: Pyrethroids have historically been classified into two groups, Type I and Type II, based upon chemical structure and neurotoxicological effect. Flumethrin is a Type II synthetic pyrethroid, which typically produce a distinct poisoning syndrome which is characterized by choreoathetosis (sinuous writhing of the whole body) and excessive salivation also known as CS syndrome. The data base of experimental toxicology studies available for flumethrin provides a robust characterization of the hazard. There are no outstanding studies according to Part 158 data requirements for a non-food use pesticide registration. In addition, numerous studies from the scientific literature that describe the pharmacodynamic and pharmacokinetic profile of the pyrethroids in general have been considered in this assessment.

Flumethrin has been evaluated for a variety of toxic effects in experimental toxicity studies. Neurobehavioral changes characteristic of Type II pyrethroids (i.e., pawing, burrowing, salivation, and coarse tremors leading to choreoathetosis (CS-syndrome)) were observed at high doses in experimental toxicology studies with flumethrin. Specifically, profuse salivation has been observed in a variety of guideline flumethrin toxicological studies. Although salivation was observed in nearly all experimental studies in all species and durations, the decreased motor activity observed in the acute neurotoxicity (ACN) study was selected as the endpoint for risk assessment. Decreased motor activity was the most sensitive endpoint identified for flumethrin and is protective of the salivation seen throughout the database. Additional effects seen in one or more studies included hind-limb swelling, digit eating, and staining. Flumethrin also produced decreased body weights, body weight gains, and food consumption in repeat dosing studies at similar doses that produced decreased motor activity in the ACN.

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. Following a single oral gavage dose, flumethrin is absorbed quickly in rats displaying decreased motor activity and increased salivation, neurotoxicity is observed within 5 hours, and rats recover within 24 hours without any persisting neurotoxic effects. This is generally consistent with the toxicity profiles for all the pyrethroids which are very similar and marked by rapid absorption, metabolism, and time-to-peak effect.

The NOAELs and LOAELs established from flumethrin single dose and repeat dosing studies show that repeat exposures do not result in lower NOAELs. Thus for purposes of endpoint selection and exposure assessment, only single day risk assessments need to be conducted.

Evidence of increased qualitative or quantitative susceptibility of the offspring was not observed in any of the available animal testing guideline toxicity studies. However, the Agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age based on the following: 1) age-dependent pharmacokinetics, supported by rat Physiologically Based Pharmacokinetic (PBPK) model predictions of a 3-fold increase of pyrethroid concentration in juvenile brain compared to adults; 2) *in vitro* pharmacodynamic (PD) data and *in vivo* data indicating similar responses between adult and juvenile rats at low doses; and 3) data indicating that the rat is a conservative model compared to the human based on species-specific pharmacodynamics of homologous sodium channel isoforms.

Quantification of dermal risks was performed using a 90-day dermal rat study with a NOAEL of 10 mg/kg/day based on loss of hair; decreased body weight and body weight gain (males); decreased erythrocytes; high stepping gait; and increased absolute spleen weight (LOAEL = 30 mg/kg/day). Quantification of incidental oral ingestion risks was performed using the rat acute neurotoxicity study with a NOAEL of 0.5 mg/kg/day based on decreased motor/locomotor activity; increased staining of the mouth, perianal, and nose; increased lacrimation; and increased salivation (LOAEL = 1 mg/kg/day). Quantification of inhalation risks is not required as handler and post-application inhalation exposure is expected to be negligible from the proposed flumethrin pet collars.

There were no treatment related increases in tumor incidences when compared to controls in both the rat chronic toxicity/carcinogenicity study and the carcinogenicity mouse study. In accordance with the Agency's 2005 Cancer Guidelines, there was no evidence of carcinogenicity in either species and this chemical is classified as "Not likely to be carcinogenic to humans".

Food Residue Profile: There are no proposed or currently registered food uses for flumethrin.

Dietary Exposure and Risk: A dietary (food + drinking water) exposure assessment is not required, since there are no proposed or currently registered food uses for flumethrin and drinking water exposure is not expected from the proposed uses.

Residential Exposure: Residential handler exposures to flumethrin pet collars may occur via the dermal route. The durations of handler exposure relevant to the proposed use pattern are short-term because the proposed pet collar has an efficacious life of 8 months (i.e., a collar would only be applied once every 8 months). However, the available toxicological data supports the conclusion that neurotoxicity from flumethrin and pyrethroids in general is associated with acute, peak exposures. As such, only single day dermal risks were assessed. No risks of concern for residential handler exposure were identified in this assessment.

Residential post-application exposures to flumethrin can also occur after collars are placed on a cat or dog via dermal and oral exposure routes. The durations of exposure relevant to the proposed use pattern are short-term, intermediate term, and chronic as flumethrin pet collars

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could potentially be used year round. However, the available toxicological data supports the conclusion that neurotoxicity from flumethrin and pyrethroids in general is associated with acute, peak exposures. As such, only single day dermal risks were assessed. Dermal post-application risks were assessed for adults and children 1 < 2 years old while oral (hand-to-mouth) post-application risks were assessed for children 1 < 2 years old. No risks of concern for residential post-application exposure were identified in this assessment.

Aggregate Risk: There are currently no registered food uses for flumethrin and drinking water exposure is not expected from the proposed pet collar uses of flumethrin; therefore, a quantitative aggregate risk assessment is not required at this time.

Occupational Exposure/Risk: For the proposed flumethrin pet collar uses, occupational handler exposures are expected to be less or at worst case equal to the residential handler exposures as this is traditionally considered a consumer product as opposed to one applied by veterinarians or professional groomers. As a result, no quantitative occupational handler exposure and risk assessment has been performed. The residential handler exposure and risk assessment is considered protective for any potential occupational handler exposures and risks.

For the proposed flumethrin pet collar uses, occupational post-application exposure could potentially occur, however; these types of exposures are not expected to be greater than residential post-application exposures (i.e., minimal and infrequent contact by a professional animal care worker is expected to occur after a collar is applied). As a result, no quantitative occupational post-application exposure and risk assessment has been performed. The residential post-application exposure and risk assessment is considered protective for any potential occupational post-application exposures and risks.

Review of Human Research: This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies (listed in Appendix B) have been determined to require a review of their ethical conduct and all of the studies utilized in this assessment have received the appropriate review.

2.0 HED Recommendations

HED has evaluated the toxicity and exposure databases for the active ingredient, flumethrin, and has conducted a human health risk assessment in support of the proposed uses. Based on this assessment, HED has determined that there are no potential risk estimates of concern for the proposed uses of flumethrin. HED recommends that the requested uses be granted.

2.1 Data Deficiencies

The following data would allow HED to refine the flumethrin risk assessment:

EXPOSURE

A flumethrin pet transferable residue study (i.e., a petting study) would allow HED to refine the residential post-application exposure and risk assessment. This study has become the standard study for use in assessing the amount of pesticide residue that is available for transfer from pets. HED encourages the registrant to submit a protocol to the Agency for review before initiation of the study.

The following data would allow HED to refine the flumethrin relative potency factor in the pyrethroid cumulative risk assessment:

TOXICOLOGY

The existing toxicology database for assessment of flumethrin as a single chemical is complete with respect to the guideline requirements for a non-food use pesticide. However, unlike most of the other pyrethroids, a specially designed functional observational battery (FOB) study is not available for use in estimating relative potency for purposes of cumulative risk assessment. Such FOB data are available for 17 other pyrethroids and these data provide the basis for high confident relative potency factors in the pyrethroid cumulative (USEPA, 2011a). As such, the data used in the estimated RPF for flumethrin does not represent such a uniform measure of potency and introduces some uncertainty in the cumulative risk assessment. In lieu of this data, the Agency used the flumethrin acute neurotoxicity study to estimate an RPF for flumethrin (see Appendix D for more details). Although the Agency believes the estimated RPF does not underestimate the contribution of flumethrin to the pyrethroid cumulative risk assessment, a flumethrin FOB study would allow the Agency to develop an RPF using a uniform measure of relative potency and thus reduce the uncertainty introduced by the lack of such data. HED encourages the registrant to develop such special FOB data. In the event that the registrant elects to develop these data, HED further encourages the submission of a protocol to the Agency for review before initiation of the study.

2.2 Tolerance Considerations

There are no established or proposed tolerances for flumethrin in or on any food or feed crops.

2.3 Label Recommendations

2.3.1 Recommendations from Residential Assessment

No label revisions are needed for residential exposure purposes and no recommendations are being made by HED.

2.3.2 Recommendations from Occupational Assessment

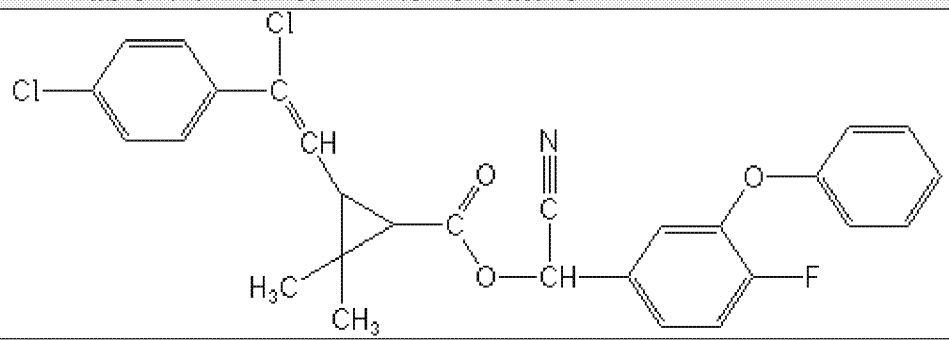
No label revisions are needed for occupational exposure purposes and no recommendations are being made by HED.

3.0 Ingredient Profile

Flumethrin is a new synthetic pyrethroid insecticide.

3.1 Structure and Nomenclature

Table 3.1: Flumethrin Nomenclature

Chemical Structure	
Common Name	Flumethrin
IUPAC name	(*RS*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-(*EZ*)-3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate
CAS Name	cyano(4-fluoro-3-phenoxyphenyl)methyl 3-[2-chloro-2-(4-chlorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate
CAS Registry Number	69770-45-2
Chemical Class	Synthetic pyrethroid

3.2 Physical/Chemical Characteristics

Table 3.2: Flumethrin Physical and Chemical Properties	
Parameter	**Value**
Molecular Weight	510.4 g/mol.
Boiling Point	>250°C
Water solubility (20°C)	9.7×10^{-5} mg/l
Solvent solubility (20°C)	No Data
Vapor pressure (25°C)	3.9×10^{-9} mm Hg
Henry's Law Constant (25°C)	4.2×10^{-8} atm-m^3/mol
Octanol/water partition coefficient	log Kow = 7.65

3.3 Summary of Existing/Proposed Uses

Flumethrin is a new active ingredient being proposed for use as an ectoparasiticide for the control of ticks, lice, and mites (pet collars) for use in cat and dog collars that also contain imidacloprid. There are two different sizes of collar being proposed both of which contain 4.5% flumethrin and 10% imidacloprid. The small collar weighs 12.5 grams and is intended for use on cats and small dogs up to 8 kg in weight. The large collar weighs 45 grams and is intended for use on dogs over 8 kg in weight. The collars have an efficacious life of 8 months. There are restrictions on the label preventing use of collars on kittens under 7 weeks of age or puppies under 10 weeks of age.

3.4 Anticipated Exposure Pathways

The Registration Division has requested an assessment of human health risk to support the proposed new uses of flumethrin in cat and dog collars. Humans are not expected to be exposed to flumethrin in their diet as the proposed pet collar uses of flumethrin are considered to be non-food uses. Drinking water exposure is also not expected based on the proposed pet collar uses of flumethrin. The proposed uses will potentially result in residential handler and post-application exposures. Additionally, there is a potential for occupational handler and post-application exposure to pet care professionals.

These are the first registrations proposed for flumethrin in the United States; therefore, this is the first risk assessment prepared by the Agency to address potential risks associated with the use of this new active ingredient.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption,

and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Flumethrin is a member of the pyrethroid class of chemicals. Pyrethroids have historically been classified into two groups, Type I and Type II, based upon chemical structure and neurotoxicological effect. Type I pyrethroids, which lack an alpha-cyano moiety, induce in rats a syndrome consisting of aggressive sparring, altered sensitivity to external stimuli, and fine tremor progressing to whole-body tremor and prostration (T-syndrome). Type II pyrethroids, which contain an alpha-cyano moiety, in rats produce a syndrome that includes pawing, burrowing, salivation, and coarse tremors leading to choreoathetosis (CS-syndrome) (Verschoyle and Aldridge 1980; Lawrence and Casida 1982). Flumethrin is a Type II synthetic pyrethroid. The adverse outcome pathway (AOP) shared by pyrethroids involves the ability to interact with voltage-gated sodium channels (VGSCs) in the central and peripheral nervous system, leading to changes in neuron firing, and ultimately neurotoxicity (see Figure 1).

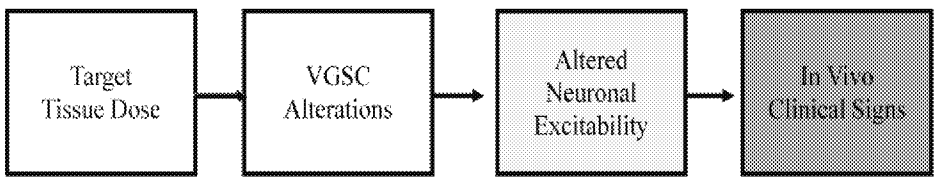


Figure 1. Adverse outcome pathway for pyrethroids

4.1 Toxicology Studies Available for Analysis

The data base of experimental toxicology studies available for flumethrin provides a robust characterization of the hazard potential for children 6 years old and older and for adults. There are no outstanding studies according to Part 158 data requirements for a non-food use pesticide registration. However, there are on-going efforts to develop data to inform the potential sensitivity of infants and younger children to pyrethroids as a class which is discussed further in Section 4.4. Despite these scientific efforts, HED is confident that it has chosen points of departure and uncertainty factors in this risk assessment which are health protective and have a strong scientific foundation.

The data from the following studies were used to evaluate the hazard potential of flumethrin:

-Developmental Rat Studies
-Developmental Rabbit Studies
-Reproduction Rat Study
-Chronic/Cancer Mouse Study
-Chronic/Cancer Rat Study
-28 Day Mouse Study
-90- Day Rat and Mouse Study
-Acute Neurotoxicity (ACN) Rat Study
-Subchronic Neurotoxicity (SCN) Rat Study
-Developmental Neurotoxicity (DNT) Rat Study
-14-day, 28-day, and 90-day Dermal Rat Study
-28-day Inhalation Rat Study
-Genotoxicity Studies
-Immunotoxicity Study
-Metabolism and Pharmacokinetics

The studies available for consideration of flumethrin toxicity provide a comprehensive database. In addition, numerous studies from the scientific literature conducted over several decades describe the pharmacodynamic and pharmacokinetic profile of the pyrethroids in general; this scientific literature has been recently reviewed by several groups (Wolansky and Harrill 2008; Weiner et. al. 2009). Although none of this literature provides any specific data on flumethrin, because of the shared toxicological properties of the members of this class of pesticides, these studies are informative in the hazard characterization of flumethrin.

4.2 Flumethrin Toxicological Profile

Flumethrin has been evaluated for a variety of toxic effects in guideline experimental toxicity studies. Neurobehavioral changes characteristic of Type II pyrethroids (e.g., pawing, burrowing, salivation, and coarse tremors leading to choreoathetosis (CS-syndrome)) were observed at high doses in experimental toxicology studies with flumethrin. Specifically, profuse salivation has been observed in the following guideline flumethrin toxicological studies: developmental rat toxicity studies; the developmental neurotoxicity study; sub-chronic rat toxicity studies; acute and sub-chronic rat neurotoxicity studies; 90-, 21-, and 14-day dermal rat toxicity studies; and chronic mouse oral toxicity studies. Although salivation was observed in nearly all experimental studies in all species and durations, the decreased motor activity observed in the acute neurotoxicity (ACN) study was selected as the endpoint for risk assessment. Decreased motor activity was the most sensitive endpoint identified for flumethrin and is protective of the salivation seen throughout the database. Additional effects seen in one or more studies included hind-limb swelling, digit eating, and staining. Flumethrin also produced decreased body weights, body weight gains, and food consumption in repeat dosing studies at similar doses that produced decreased motor activity in the ACN. Regarding gender, males were found to be more sensitive throughout the database (i.e., males were found to have lower NOAELs versus females in the mouse carcinogenicity, rat subchronic, dermal, reproductive, ACN, and SCN studies).

The potential reproductive toxicity of flumethrin was examined in a multi-generation reproduction study in the rat. Parental toxicity was expressed as reductions in pituitary weights (F1 generation) for males at the low dose and reduction in liver weights in females (F0 and F1 generations) at the mid-dose. Offspring toxicity was expressed by decreased body weight, decreased rearing indexes, and deaths at post natal days 0-4, all occurring at the high dose. Developmental studies in both rats and rabbits had NOAELs based on increased salivation, decreased body weight gains and food consumption. Maternal effects showed slight increases in abortions and increased swelling of the limbs at the highest dose tested.

The pharmacokinetics of flumethrin is similar to other pyrethroids, i.e., rapid absorption and clearance. Following a single oral dose, flumethrin was excreted mainly via the feces (68%) within 24 hours. In radiolabeled flumethrin studies, absorbed radioactivity calculated as the sum of urine, bile and body tissues accounts for 75% of the given dose in bile duct-cannulated rats, indicating a high level of absorption following an oral dose. The rapid absorption was also observed in an exploratory PK study where the maximum plasma levels of flumethrin were found at 2 and 4 hours after administration for each dose level.
The acute toxicity profile of flumethrin consists of mild toxicity via the oral, dermal, and inhalation routes of exposure (Category II). The eye irritation study was indicates that the technical is an amorphous glass-like solid that does not exist as a fine powder at room temperature and so cannot be tested by this exposure route. A waiver was granted for the eye irritation study with assignment to toxicity category IV by this exposure route. Flumethrin was assigned to Category IV as a skin irritant. The dermal sensitizer study was deemed unacceptable but can be upgraded to acceptable with adequate reporting classification of the test material.

4.2.1 Critical Duration of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. Following a single oral gavage dose, flumethrin is absorbed quickly in rats displaying decreased motor activity and increased salivation, neurotoxicity is observed within 5 hours, and rats recover within 24 hours without any persisting neurotoxic effects. This is generally consistent with the toxicity profiles for all the pyrethroids which are very similar and marked by rapid absorption, metabolism, and time-to-peak effect. The NOAELs and LOAELs for both motor activity changes and decreases in body weight established from results of experimental toxicity studies with flumethrin are remarkably consistent across durations of exposure ranging from a single dose up to 2-years of dosing (see Table 4.3).

Table 4.3: Experimental Toxicology Studies with Similar Results			
Study	**Duration**	**Study findings (mg/kg/day)**	
Acute Neurotoxicity	Acute, single exposure	NOAEL = 0.5	LOAEL = 1.0
Developmental neurotoxicity	86 days	NOAEL = 1.0	LOAEL = 2.0
Sub-chronic mouse	90 day	NOAEL = 0.9	LOAEL = 1.4
Sub-chronic rat	90 day	NOAEL = 0.7	LOAEL = 2.9
Sub-chronic neurotoxicity	90 day	NOAEL = 1.0	LOAEL = 2.6
Reproductive toxicity	120 days	NOAEL = 0.2	LOAEL = 2.4
Chronic-carcinogenicity rat	2-year	NOAEL = 0.7	LOAEL = 2.0
Carcinogenicity mouse	2-year	NOAEL = 0.4	LOAEL = 2.0

Looking at the NOAELs and LOAELs established from flumethrin single dose and repeat dosing studies it is apparent that repeat exposures do not result in lower NOAELs. This is consistent with the general kinetic profile for the pyrethroids. The LOAEL from the ACN (1.0 mg/kg) is the same as chronic 2-year cancer study (LOAEL 2.0 mg/kg/day). Therefore, the endpoint from the acute study is protective of the endpoints from the repeat dosing studies. Thus for purposes of endpoint selection and exposure assessment, only single day risk assessments need to be conducted.

4.3 Pyrethroid Pharmacokinetic and Pharmacodynamic Profile

The extensive body of scientific literature on the pyrethroids provides a unique insight into the contributions of pharmacokinetics (PK) and pharmacodynamics (PD) to the general toxicity profile of this class of chemicals. This information also provides valuable insight into the potential age-related differences in toxicity for the pyrethroids. The following sections discuss the specific issues related to pyrethroid pharmacokinetics, pyrethroid pharmacodynamics, and age-related differences in pyrethroid toxicity.

4.3.1 Pharmacokinetics

Pharmacokinetics can be defined as what the body does to the chemical; in this case, how pyrethroids are distributed and eliminated following exposure. Specific to pyrethroids, PK refers to the process(es) which determine the concentration of the pyrethroids reaching sodium channels. The underlying pharmacokinetics of pyrethroids is an important determinant of their toxicity because the concentration of pyrethroid at the sodium channel relates to the extent of toxicity; greater pyrethroid concentration translates as increased neurotoxicity. Two physiological processes that significantly contribute to the PK include metabolism and partitioning. Carboxylesterases and P450 enzymes are the two major enzyme families responsible for metabolism of pyrethroids. It is the ontogeny of these enzymes that accounts for the age-related sensitivity observed after pyrethroid exposures. With respect to the partitioning of pyrethroids within the body, pyrethroids are highly lipophilic and preferentially deposit in fatty tissue such as adipose compared to leaner tissues such as muscle. Pyrethroid residues in fatty tissue are not available to interact with the VGSCs in vital tissues and therefore do not contribute to overall toxicity.

Physiologically-based pharmacokinetic (PBPK) models, designed to predict pyrethroid concentration in tissues following *in vivo* exposure, have recently been developed by the Agency. The Agency has determined that the important PK properties relevant for the metabolism and distribution of pyrethroids in the body are sufficiently similar for members of this class such that using a 'generic' or family model structure for this class is scientifically appropriate. In other words, due to the similarities in the PK profiles of pyrethroids, a single model structure is able to predict the tissue dose based on the pharmacokinetics of every member of the class. The family modeling approach was presented to and supported by the FIFRA SAP (USEPA 2007).

In 2011 the Agency conducted an analysis of the toxicokinetic profile of pyrethroids as a class. Several studies in this analysis indicate that there are age-dependent pharmacokinetic differences for the pyrethroids (i.e., there are differences in the ability of adults and juveniles to metabolize pyrethroids). The enzymes which metabolize and detoxify the pyrethroids are present in rats and humans at birth (Koukouritaki et. al. 2004; Yang et. al. 2009). As a result, both juveniles and adults are able to tolerate low doses of pyrethroids when the internal dose, or the amount of pyrethroid at the sodium channel, is low. However, the activity of these enzymes increases with age, conveying in adults a greater capacity to detoxify pyrethroids compared to juveniles (Anand et. al. 2006; de Zwart et. al. 2008; Yang et. al. 2009). For example, the rate of *in vitro* metabolism of deltamethrin by plasma carboxyesterases, hepatic carboxyesterases, and hepatic microsomes are at least 6 times higher for PND 90 rats compared to PND 10 rats (Anand et. al. 2006). As a consequence, higher internal doses (i.e., those associated with high doses in experimental toxicology studies) overwhelm the clearance mechanisms in juveniles but because adults have greater enzyme activity, they are able to tolerate higher doses prior to the onset of toxicity. As a matter of perspective, the anticipated exposures from typical dietary or residential activities are not expected to overwhelm the premature metabolic systems in juveniles.

Predictive PBPK models have recently been developed to describe the PK of a few pyrethroids (Mirfazaelian et. al. 2006; Godin et. al. 2010). Among these is an age-dependent model developed by the Agency which is capable of predicting the concentration of deltamethrin in the brains of rats at multiple ages (Tornero-Velez et. al. 2010). The brain is considered the primary target organ for pyrethroids and increased pyrethroid concentrations are correlated with increasing systemic toxicity. This model predicts that, compared to adult rats (i.e., 90-days old), equivalent brain concentrations of deltamethrin would be achieved with a 3.8X fold lower oral dose in 10-day old rats and 2.5X lower dose in 21-day old rats (Tornero-Velez et. al. 2010). For example, a 1 mg/kg dose in the adult is equivalent to a 0.26 mg/kg dose (≈1 mg/kg÷3.8mg/kg) in the 10-day old rats and to a 0.4 mg/kg (≈1 mg/kg÷2.5mg/kg) dose in a 21-day old rat. The difference between a 3.8- and a 2.5-fold dose is within background variability of the model. As a result, the Agency concludes that juvenile rats are 3x more sensitive than adults with respect to pyrethroid pharmacokinetics.

4.3.2 Pharmacodynamics

Pharmacodynamics (PD) can be defined as the changes that chemicals cause to the body, in this case, how pyrethroids interact with the sodium channels. Substantial evidence from *in vitro* and *in vivo* studies support the AOP illustrated in Figure 1 above as well as disruption of sodium

channels by pyrethroids as an early key event in this AOP (Lund and Narahashi 1982; Salgado et. al. 1989; Song and Narahashi 1996; Tabarean and Narahashi 1998; Soderlund et. al. 2002 (review)). As a new active ingredient, there are no recent studies for flumethrin which provide information on how flumethrin interacts with the sodium channels. However, there are several recent studies which provide information on a variety of other pyrethroids. Choi and Soderlund (2006) examined interactions of several pyrethroids with mammalian VGSCs expressed in *Xenopus* oocytes. With respect to altered neuronal excitability, Type I pyrethroids cause slight prolongations of the sodium current tails (e.g. ~20 ms), often resulting in long trains of action potentials. In contrast, Type II pyrethroids significantly prolong sodium current tails (e.g. 200ms to minutes) typically resulting in increased resting membrane potential and ultimately causing depolarization dependent action potential block. Cao et. al. (2011a) measured Na influx in primary cultures of mammalian (mouse) neurons and demonstrated that pyrethroids caused increases in Na influx in this model; this confirms the ability of pyrethroids to interact with VGSC in intact mammalian neurons. An additional study by Cao et. al. (2011b) demonstrated that the interaction of pyrethroids with VGSC caused changes in neuronal excitability that resulted in calcium influx into intact mouse neurons.

HED would prefer to use an early key event in the AOP for pyrethroids in selection of points of departure. However, i*n vivo* techniques used to detect VGSC alteration and altered neuronal excitability are not practical for use in risk assessment at this time and approaches for extrapolating *in vitro* findings to *in vivo* measures are not yet developed. As such, the Agency is focusing its efforts for all pyrethroids in hazard characterization and identification on the apical endpoint (i.e., changes in neurobehavior in laboratory animals). Neurotoxicity resulting from pyrethroids are generally characterized by tremors, hyper- or hypothermia, heightened response to stimuli, salivation, tremors and convulsions (Nemec 2006; Wolansky and Harrill 2008; Breckenridge et. al. 2009).

In contrast to the age-related PK differences identified in the 2011 analysis, PD contributions to pyrethroid toxicity are not age-dependent even though there are several variations of sodium channels, called isoforms, which are differentially expressed by tissue and age. Due to the nature of the interaction of pyrethroids with sodium channels, it is difficult to obtain dynamic information *in vivo*. To date, a readily useable biomarker of *in vivo* pyrethroid interaction with sodium channels has not been identified, making it impractical to determine the isoform combinations that are present and being acted upon by pyrethroids. Therefore, much of the information available to the Agency to characterize the PD relationship between pyrethroids and sodium channels has been derived from *in vitro* studies using frog oocytes or nervous cells artificially grown in media. While these *in vitro* techniques do not provide direct quantitative measure of *in vivo* pyrethroid activity, they consistently and qualitatively demonstrate that channel isoforms expressed in juveniles are not more sensitive to pyrethroid perturbation compared to isoforms expressed in adults and that, pharmacodynamically, the rat is a conservative model for humans. For example, Meacham et al. (2008), compared the sensitivity of an adult isoform and a juvenile isoform expressed in frog oocytes to deltamethrin. The isoforms had comparable responses at environmentally relevant concentrations (<500 nM) of deltamethrin, suggesting a lack of PD difference between juveniles and adults at low exposure levels. In addition, in a direct comparison of a homologous rat and human VGSC isoform, NaV1.3, Tan and Soderlund, (2009) found the rat isoform was 4-fold more sensitive than the

equivalent human sodium channel to the pyrethroid tefluthrin (Tan and Soderlund 2009), suggesting the rat is a highly sensitive model and extrapolations from the rat would be protective of human health. The occurrence and ontogeny of voltage-gated sodium channels in humans is not well characterized compared to the rat. However, based on the comparable function and distribution of sodium channels between the species, the rat is an appropriate surrogate for the evaluation of human PD (Goldin et. al. 2000; Goldin 2002). As a result, the Agency concludes that juvenile rats are not more sensitive than adults with respect to pyrethroid pharmacodynamics.

4.4 Consideration of Toxicity to Children

Food Quality Protection Act (FQPA) considerations do not apply to flumethrin for the proposed (non-food) use patterns described in this risk assessment. However, since flumethrin is a pyrethroid and exposure to children under <6 years old is expected, flumethrin must be considered in the greater context of the pyrethroids as a class. The Agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age based on the increased quantitative susceptibility seen in the scientific literature related to pyrethroid pharmacokinetics. This is consistent with the Agency's 2011 analysis and is supported by rat PBPK model predictions of a 3-fold increase of deltamethrin concentrations in the juvenile brain compared to adults (see Section 4.3.1). The PK of pyrethroids as a group is sufficiently similar that significant deviations from the 3-fold increase of deltamethrin concentrations are not expected for other pyrethroids. As noted in Section 4.3.2, juveniles are not more sensitive than adults with respect to pyrethroid pharmacodynamics and thus no uncertainty factor is needed for PD considerations.

4.4.1 Completeness of the Toxicology Database

There are no residual uncertainties with regard to the flumethrin toxicological database. Flumethrin has all of the required toxicity studies to assess the current non-food use.

4.4.2 Evidence of Neurotoxicity

There are no residual uncertainties with regard to evidence of neurotoxicity for flumethrin. Flumethrin, like other pyrethroids, causes neurotoxicity from interaction with sodium channels leading to clinical signs of neurotoxicity. Neurotoxicity was consistently observed throughout the database in a dose-dependent manner in most all of the studies conducted. The mode of action is fully characterized and indications of neurotoxicity included salivation typical of Type II pyrethroid compounds.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Based on the flumethrin-specific data and the extensive body of peer-reviewed literature on pyrethroids available, the Agency reached a number of conclusions including the following:

- The Agency has no residual uncertainties regarding age related sensitivities for women of child bearing age as well as for all adult populations and children > 6 years of age,

based on the absence of pre-natal sensitivity observed in 76 guideline studies for 24 pyrethroids, the scientific literature, and the flumethrin guideline toxicological studies.
- Although the flumethrin toxicological database was not considered in the 2011 analysis, the flumethrin developmental, reproductive, and DNT toxicity studies are consistent with other members of the pyrethroid class in that no evidence of increased quantitative or qualitative susceptibility was observed in these studies.
- No evidence of increased quantitative or qualitative susceptibility was seen in the pyrethroid scientific literature related to pharmacodynamics.
- The Agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age based on the increased quantitative susceptibility seen in the scientific literature related to pyrethroid pharmacokinetics.

The Agency is aware that additional *in vitro* and *in vivo* studies are currently being conducted that could potentially inform a number of issues related to pyrethroid toxicity as a class. In 2010, the Agency requested proposals for study protocols which could identify and quantify potential juvenile sensitivity and received a single, coordinated response from the Pyrethrin and Pyrethroids Working Group (PPTWG), a conglomerate of pyrethroid registrants. The PPTWG protocol was reviewed during a July 2010 FIFRA SAP meeting[1]. Based on comments from the SAP, the initial study proposal was refined. At present time, pesticide registrants and product formulators have come together as Council for the Advancement of Pyrethroid Human Risk Assessment (CAPHRA) and plan on doing the following: 1) conducting *in vitro* studies demonstrating the interaction of pyrethroids exogenously expressed rat and human VGSCs in *Xenopus* oocytes; 2) conducting *in vitro* studies demonstrating interaction of pyrethroids in rat neurolemma cells; 3) developing rat and human PBPK models, including additional pharmacokinetic data; and 4) conducting *in vivo* behavioral testing using auditory startle testing in rats. As these data becomes available, the Agency will determine whether re-evaluation of the age-related sensitivity of pyrethroids is appropriate.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to residential exposure. The residential exposure assessment is based on conservative, health-protective assumptions that ensure that exposures to the proposed flumethrin pet collars are not underestimated.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

The details for selecting toxicity endpoints and points of departure (PODs) are presented in Appendix A2. Based on the proposed use pattern for flumethrin in pet collars, the expected exposure profile will be for dermal and incidental oral exposures. Therefore, acute dietary and inhalation endpoints were not established.

Acute Dietary: The current proposed use is for a non-food pet collar use. Acute dietary PODs have not been established for this risk assessment.

[1] http://www.epa.gov/scipoly/sap/meetings/2010/072310meeting.html

Short-term Dermal: Quantification of dermal risks was performed using a 90-day dermal rat study with a NOAEL of 10 mg/kg/day based on loss of hair; decreased body weight and body weight gain (males); decreased erythrocytes; high stepping gait; and increased absolute spleen weight (LOAEL = 30 mg/kg/day).

Short-term Incidental Oral: Quantification of incidental oral ingestion risks was performed using the rat acute neurotoxicity study with a NOAEL of 0.5 mg/kg/day based on decreased motor/locomotor activity; increased staining of the mouth, perianal, and nose; increased lacrimation; and increased salivation (LOAEL = 1 mg/kg/day).

Short-term Inhalation: Quantification of inhalation risks is not required as handler and post-application inhalation exposure is expected to be negligible from the proposed flumethrin pet collars.

4.5.2 Recommendation for Combining Routes of Exposure for Risk Assessment

HED combines risk values resulting from separate exposure pathways when it is likely they can occur simultaneously based on the use pattern, the behavior associated with the exposed population, and the hazard associated with the points of departure. For flumethrin, the points of departure are based on different effects and thus it is not appropriate to combine the dermal and oral exposure scenarios.

4.5.3 Cancer Classification and Risk Assessment Recommendations

In neither a rat chronic toxicity/carcinogenicity study nor a carcinogenicity mouse study, both conducted with adequate doses, were there treatment related increases in tumor incidences when compared to controls. In accordance with the Agency's 2005 Cancer Guidelines, there was no evidence of carcinogenicity in either species and this chemical is classified as "Not likely to be carcinogenic to humans".

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4.5.4 Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5: Summary of Toxicological Doses and Endpoints for Flumethrin

Exposure Scenario	Dose Used in Risk Assessment, UF	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term (1-30 days) Incidental Oral	NOAEL= 0.5 mg/kg/day	UF_A = 10x UF_H = 10x, UF_{QS} = 3x	Residential LOC for individuals < 6 years old = 300	Acute Neurotoxicity Study LOAEL= 1 mg/kg/day in males based on ↓motor/locomotor activity, ↑staining of mouth, perianal, nose, ↑lacrimation, salivation at ↑doses
Short-Term (1-30 days) Dermal	NOAEL = 10 mg/kg/day	UF_A = 10x UF_H = 10x UF_{QS} = 3x	Residential LOC for individuals < 6 years old = 300 Residential LOC for individuals > 6 years old = 100 Occupational LOC = 100	90-day Dermal Study LOAEL=30 mg/kg/day Based on loss of hair; ↓BW and ↓BWG (M), ↓erythrocytes, high stepping gait, ↓ABS spleen wt,
Short-Term (1-30 days) Inhalation	N/A	N/A	N/A	N/A
Cancer (oral, dermal, inhalation)	**Classification:** "Not likely" to be carcinogenic in humans			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{QS} = to account for the quantitative susceptibility to children <6 years of age. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

5.0 Dietary Exposure and Risk Assessment

5.1 Food Residue Profile

There are no proposed or currently registered food uses for flumethrin.

5.2 Water Residue Profile

Drinking water exposure is not expected based on the proposed pet collar uses of flumethrin.

5.3 Dietary Risk Assessment

A dietary (food + drinking water) exposure assessment is not required, since there are no proposed or currently registered food uses for flumethrin and drinking water exposure is not expected from the proposed uses.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Residential handler exposures to the proposed flumethrin pet collars may occur via the dermal route while the collars are placed on a cat or dog. Additionally, residential post-application exposures to flumethrin can also occur after collars are placed on a cat or dog via dermal and oral exposure routes. In assessing these exposures, the *Health Effects Division's 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment: Treated Pets* was used.

Some of the data included in the Treated Pet SOP are proprietary and thus are subject to the data protection provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

6.1 Residential Handler Exposure and Risk

Residential handler exposures to the proposed flumethrin pet collars may occur via the dermal route while the collars are placed on a cat or dog. Residential handler inhalation exposure is expected to be negligible from flumethrin pet collars and thus a quantitative assessment was not performed. Based on the proposed flumethrin pet collar label, HED has assumed that the proposed pet collars are mainly directed towards homeowner use. As a result, a dermal residential handler exposure assessment was performed for homeowners applying the collar to a cat or dog. The durations of handler exposure relevant to the proposed use pattern are short-term because the proposed pet collar has an efficacious life of 8 months. However, the available toxicological data supports the conclusion that neurotoxicity from flumethrin and pyrethroids in general is associated with acute, peak exposures (i.e., every day is a new day). As such, only single day dermal risks were assessed. Dermal handler risks were assessed only for adults.

No chemical-specific unit exposure data were provided in support of this submission and there are currently no surrogate exposure data available for applying pet collars. As a result, HED used exposure data described in the 2012 Treated Pet SOP for spot-on applications (MRID 44433303) as a health protective surrogate to estimate handler exposures for applying collars. These unit exposures were based on residential handlers wearing short pants, short-sleeved shirt, and no gloves. In addition to this data, exposure algorithms (see Appendix C) and other standard assumptions (e.g., number of pets treated) were taken from the 2012 Treated Pet SOP.

HED's level of concern for adult residential handlers is equal to an MOE of 100. All residential handler dermal exposure scenarios do not exceed HED's level of concern (i.e., MOEs ≥ 100). Handler exposure and risks are summarized in Table 6.1.1.

Table 6.1.1: Residential Handler Exposure and Risk for Flumethrin

Scenario	Dermal Unit Exposure [a] (mg/lb ai)	Application Rate [b]		Amount Treated [c]	Dermal Dose [d] (mg/kg/day)	Dermal MOE [e]
Applying Pet Collars	120	Small collar (12.5 gram)	0.00124 lb ai/collar	2 pets	0.0037	2,700
		Large collar (45 gram)	0.00446 lb ai/collar		0.013	750

a. Data taken from 2012 Treated Pets SOP (MRID 44433303)
b. Small collar application rate: 12.5 gram collar x 4.5% flumethrin x 0.0022 lb/g = 0.00124 lb ai flumethrin per collar
Large collar application rate: 45 gram collar x 4.5% flumethrin x 0.0022 lb/g = 0.00446 lb ai flumethrin per collar
c. Data from the American Pet Products Manufacturers Association (APPA) 2011-2012 National Pet Owners Survey as presented in the 2012 Treated Pets SOP
d. Dermal Dose (mg/kg/day) = unit exposure (mg/lb ai) * application rate * amount treated/ body weight (80 kg).
e. Dermal MOE = NOAEL (10 mg/kg/day)/Dermal Dose

6.2 Residential Postapplication Exposure and Risk

Residential post-application exposures to flumethrin can also occur after collars are placed on a cat or dog via dermal and oral exposure routes. Residential postapplication inhalation exposure is expected to be negligible from flumethrin pet collars and thus a quantitative assessment was not performed. The durations of postapplication exposure relevant to the proposed use pattern are short-term, intermediate-term, and chronic as flumethrin pet collars could potentially be used year round. However, the available toxicological data supports the conclusion that neurotoxicity from flumethrin and pyrethroids in general is associated with acute, peak exposures. As such, only single day dermal risks were assessed. Dermal post-application risks were assessed for adults and children 1 < 2 years old while oral (hand-to-mouth) post-application risks were assessed for children 1 < 2 years old.

A pet transferable residue study (i.e., a petting study) was not submitted for flumethrin. Bayer did submit chemical-specific data (MRID 48240140 provides a summary of all of the data) related to the amount of flumethrin that was released from the small and large collars over the life of the collar (i.e., 8 months or 240 days). Depending on the study, measurements were taken at 30, 60, 90, and 240 days after applying the collar and these studies were performed on cats (small collars) and dogs (large collars). This data does not specifically provide the surface residues of flumethrin on a cat or dog nor does it provide the amount of flumethrin that could be transferred to a person who contacts a treated cat or dog. Since acute exposures are most toxicologically relevant for flumethrin, HED is most interested in flumethrin residues for the first few days after the collar is applied. The available studies did not collect any data from these days so for this assessment HED has focused only on the data that was collected at 30 days. Table 6.2a presents a summary of this data.

Table 6.2.a: Summary of Flumethrin Released from Small and Large Pet Collars (MRID 48240140)

Study Number	Collar Size	Study Period	Amount of Flumethrin Released Over Study Period (mg) [a]	Amount of Flumethrin Released per Day (mg/day) [b, c]	Average Flumethrin Released per Day (mg/day)
146.164	Small	30	42.43	1.41	0.94
146.747			13.7	0.46	
146.165	Large		87.49	2.92	2.39
146.737			55.9	1.86	

a. As summarized in MRID 48240140
b. Amount of flumethrin released per day (mg/day) = Amount of flumethrin released over study period (mg) / Study Period (days)
c. Assumes the release rate of flumethrin from the collar is consistent across the first 30 days

Using this data, along with some standard assumptions from the 2012 Treated Pet SOP (e.g., pet surface area, fraction of application rate available for transfer), HED estimated transferable residues by the equation presented below.

$$TR\ (mg/cm2) = \{[RR\ (mg/day) * 7\ days] / Animal\ SA\ (cm2)\} * F_{AR}$$

Where:

TR	=	Transferable Residue (mg/cm2)
RR	=	Release Rate (mg/day)
Animal SA	=	Animal Surface Area (cm2)
F_{AR}	=	Fraction Application Rate Available (F_{AR})

Because of the limitations of the available data, HED assumed the release rate of flumethrin from the collar was consistent across the first 30 days. However, pesticide release rates for pet collars are typically higher in the initial days and weeks after application. In order to be protective of this possibility, HED assumed that the Day 0 transferable residue would be the total of the first 7 days of released flumethrin. In addition to the estimated transferable residues, HED also used exposure algorithms (see Appendix C) and other standard assumptions (e.g., transfer coefficients, exposure time, fraction of pesticide on hands, hand-to-mouth events) taken from the 2012 Treated Pet SOP.

HED's levels of concern for residential postapplication adult and children exposures are equal to MOEs of 100 and 300, respectively. All residential postapplication dermal and incidental oral exposure scenarios do not exceed HED's level of concern (i.e., adult MOEs ≥ 100 and children MOEs ≥ 300). Postapplication dermal and incidental oral exposure and risks are summarized in Table 6.2.b and 6.2.c, respectively.

Table 6.2.b: Postapplication Dermal Exposure and Risk for Flumethrin

Animal Surface Area		TR [b] (mg/cm^2)	Transfer Coefficient (cm^2/hr)	ET (hrs)	BW (kg)	Dose [c] (mg/kg/day)	Dermal MOE [d]
Adults							
Small Cat	1,500	0.000087	5200	0.77	80	0.0044	2300
Large Cat	4,000	0.000033				0.0016	6100
Small Dog	3,000	0.000044				0.0021	4600
Medium Dog	7,000	0.000048				0.0024	4200
Large Dog	11,000	0.000030				0.0015	6600
Children (1 < 2 years old)							
Small Cat	1,500	0.000087	1500	1	11	0.012	870
Large Cat	4,000	0.000033				0.0045	2200
Small Dog	3,000	0.000044				0.0060	1700
Medium Dog	7,000	0.000048				0.0065	1500
Large Dog	11,000	0.000030				0.0041	2400

a. Small cat TR= [(0.94 mg/day * 7 days) / 1500 cm^2] * 2%
Large cat TR= [(0.94 mg/day * 7 days) / 4000 cm^2] * 2%
Small dog TR= [(0.94 mg/day * 7 days) / 3000 cm^2] * 2%
Medium dog TR= [(2.39 mg/day * 7 days) / 7000 cm^2] * 2%
Large dog TR= [(2.39 mg/day * 7 days) / 11000 cm^2] * 2%
b. Dermal Dose (mg/kg/day) = TR (mg/cm2) * TC (cm^2/hr) * ET (hrs) / BW (kg)
c. Dermal MOE = NOAEL (10 mg/kg/day)/Dermal Dose

Table 6.2.c: Postapplication Incidental Oral (Hand-to-Mouth) Exposure and Risk for Flumethrin												
Dermal Exposure (mg)		$F_{ai\ Hands}$	SA Hands (cm^2)	HR [a] (mg/ cm^2)	FM (fraction/ event)	ET (hrs)	N_replen	SE	$Freq_{HTM}$	BW (kg)	Dose [b] (mg/kg/day)	Oral MOE [c]
Small Cat	0.14	0.039	150	0.000018	0.13	1	4	0.48	20	11	0.00012	4300
Large Cat	0.051			0.0000066							0.000045	11000
Small Dog	0.068			0.0000088							0.000058	8600
Medium Dog	0.074			0.0000097							0.000064	7900
Large Dog	0.047			0.0000061							0.000041	12000

a. $[HR = DE * Fai_{hands}] / 2 * SA_H$
b. Oral Dose = $[HR * (F_M * SA_H) * (ET * N\_Replen) * (1- (1- SE)^{(Freq\_HtM/N\_Replen)})] / BW$
c. Oral MOE = NOAEL (0.5 mg/kg/day)/Dermal Dose

6.3 Combined Residential Risk Estimates

HED combines risk values resulting from separate exposure pathways when it is likely they can occur simultaneously based on the use pattern, the behavior associated with the exposed population, and the hazard associated with the points of departure. For flumethrin, the points of departure are based on different effects and thus it is not appropriate to combine the dermal and oral exposure scenarios.

7.0 Aggregate Exposure/Risk Characterization

There are currently no registered food uses for flumethrin and drinking water exposure is not expected from the proposed pet collar uses of flumethrin; therefore, a quantitative aggregate risk assessment is not required at this time.

8.0 Cumulative Exposure/Risk Characterization

The Agency is required to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The Agency has determined that the pyrethroids and pyrethrins share a common mechanism group (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). The members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. The cumulative risk assessment for the pyrethroids/pyrethrins was published on Nov. 9, 2011 (USEPA, 2011a) and is available at http://www.regulations.gov; EPA-HQ-OPP-2011-0746. No cumulative risks of concern were identified allowing the Agency to consider new uses for pyrethroid actives. For information regarding EPA's efforts to evaluate the risk of exposure to pyrethroids, refer to http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.

As a new active ingredient, flumethrin was not currently included in the initial common mechanism grouping (CMG) science policy document from 2008 and was not assessed in the November 2011 pyrethroid cumulative risk assessment. However, the Agency has determined based on its chemical structure and based on the observation of neurobehavioral effects consistent with Type II pyrethroids, that flumethrin should be included in the CMG for this class of pesticides. As such, the Agency must consider the potential contribution of flumethrin to the cumulative risk assessment. As part of the assessment for the proposed flumethrin pet collar

uses, the Agency performed a quantitative analysis and determined that the proposed flumethrin pet collar use will not significantly contribute to or change the overall findings in the pyrethroid cumulative risk assessment. That analysis is summarized in Appendix D.

9.0 Occupational Exposure/Risk Characterization

Based on the proposed flumethrin pet collar uses, there is potential for both occupational handler and occupational post-application exposure to occur.

9.1 Occupational Handler Exposure and Risk

For the proposed flumethrin pet collar uses, occupational handler exposures are expected to be less or at worst case equal to the residential handler exposures as this is traditionally considered a consumer product as opposed to one applied by veterinarians or professional groomers. As a result, no quantitative occupational handler exposure and risk assessment has been performed. The residential handler exposure and risk assessment (see Section 6.1) is considered protective for any potential occupational handler exposures and risks.

9.2 Occupational Post-Application Exposure and Risk

For the proposed flumethrin pet collar uses, occupational post-application exposure could potentially occur; however, these types of exposures are not expected to be greater than residential post-application exposures (i.e., minimal and infrequent contact by a professional animal care worker is expected to occur after a collar is applied). As a result, no quantitative occupational post-application exposure and risk assessment has been performed. The residential post-application exposure and risk assessment (see Section 6.2) is considered protective for any potential occupational post-application exposures and risks.

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Appendix A: Flumethrin Toxicity Profiles

A.1 Toxicology Data Requirements

Guideline Number and Toxicity Study		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	no
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Sub-chronic (Rodent)	CR	yes
870.3150	Oral Sub-chronic (Non-Rodent)	CR	no
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	yes	yes
870.3465	90/28-Day Inhalation	CR	yes
870.3700	Developmental Toxicity (Rodent)	yes	yes
870.3700	Developmental Toxicity (Non-rodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100	Chronic Toxicity (Rodent)	CR	no
870.4100	Chronic Toxicity (Non-rodent)	no	yes
870.4200	Oncogenicity (Rat)	CR	no
870.4200	Oncogenicity (Mouse)	CR	yes
870.4300	Chronic/Oncogenicity	CR	yes
870.5100	Mutagenicity: Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity: Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity: Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity: Structural Chromosomal Aberrations	yes	yes
870.5500	Mutagenicity: Other Genotoxic Effects	yes	yes
870.5550	Mutagenicity: Other Genotoxic Effects	yes	no
870.6100	Acute Delayed Neurotoxicity (Hen)	CR	--
870.6100	90-Day Neurotoxicity (Hen)	CR	--
870.6200	Acute Neurotoxicity Screening Battery (Rat)	yes	yes
870.6200	90 Day Neuro. Screening Battery (Rat)	yes	yes
870.6300	Developmental Neurotoxicity	CR	yes
870.7485	General Metabolism	CR	yes
870.7600	Dermal Penetration	CR	no
870.7800	Immunotoxicity	yes	yes

--Not applicable

Appendix A.2. Toxicity Profiles

Table A.2.1: Acute Toxicity Profile – Flumethrin (PC 036007)				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral, rat	48240203	LD_{50} Females = 175 mg/kg	II
870.1100	Acute oral, rat	48240204	LD_{50} Males > 100 mg/kg LD_{50} Females = 100 mg/kg	II
870.1200	Acute dermal, rat	48240206	LD_{50} Males = 1998 mg/kg LD_{50} Females = 1436 mg/kg	II
870.1300	Acute inhalation, rat	48240208	LC_{50} Males > 0.585 / <0.812 mg/L LC_{50} Females > 0.277 / <0.585 mg/L	II
870.2400	Acute eye irritation, rabbit	48240211	Waiver requested	IV
870.2500	Acute dermal irritation, rabbit	48240213	Slight irritant; PII=0.25 Bruising observed one animal at 1 hr.	IV
870.2600	Skin sensitization, guinea pig	48240214	Not Determined	Unacceptable

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.3100	Subchronic (Oral) Toxicity - Rodent	48240222 (1995) rat Acceptable/guideline 0, 10, 40, 160 ppm (rat) M: 0, 0.7, 2.9, or 11.9 mg/kg/day F: 0, 0.8, 3.4, 13.0 mg/kg/day	NOAEL- 0.7/0.8 mg/kg/day (M/F) LOAEL – 2.9/3.4 mg/kg/day (M/F), ↑extramedullary hematopoiesis; ↓hemosiderin storage; labored breathing; ↑salivation (F); shoulder wounds (M)
		48240224 (1998) mice Acceptable/guideline (mice) 0, 5, 10, **60, 120, 240, 480** ppm **(95.1%, T0059204)** M: 0, 9.9, 20.8, 42.2 mg/kg/day F: 0, 13.2, 26.5, 56.0 mg/kg/day (94.4%, T4060297) M: 0, 0.9, 1.9 mg/kg/day F: 0, 1.4, 2.5 mg/kg/day	NOAEL - 0.9/1.9 (M/F) LOAEL - 1.4/2.5 mg/kg/day, piloerection, dermal lesions, mild hyperkeratosis and acanthosis, emaciation, and mortality at higher doses
870.3250	90 Day Dermal Toxicity - Rat	48240216 (2008) Acceptable/guideline 0, 10, 30, or 80 mg/kg/day	NOAEL - 10 mg/kg/day LOAEL - 30 mg/kg/day, loss of hair; ↓BW and ↓BWG (M), ↓erythrocytes, high stepping gait, ↓ABS spleen wt
870.3200	28 Day Dermal Toxicity - Rat	48240217 (2006) Acceptable/non-guideline 0, 100, 150, 200 mg/kg/day	NOAEL – not established, insufficient number of animals. Clinical signs: bloody muzzle, sunken flanks, reduced motility, high-stepping gait, labored breathing, diarrhea, narrowed eyelids, ↑salivation
	14 Day Dermal Toxicity - Rat	48240218 (2007) Acceptable/non-guideline 0, 10, 30, 100 mg/kg/day	NOAEL – not established, insufficient number of animals. Clinical signs: bloody muzzles, bleedings on nose, hunched backs, reduced motility, high-stepping gait, labored breathing, narrowed eyelids, ↑salivation
870.3700a	Prenatal Developmental Toxicity - Rat	48240225 (1999) Acceptable/guideline 0, 0.75, 2, 5 mg/kg/day	**Maternal** NOAEL – 0.75 mg/kg/day. LOAEL - 2 mg/kg/day, ↓ *H2O, ↓feces, ↓BW/BWG, ↓gravid uterine wt, ↓food consumption*; ↓BW **Developmental** NOAEL – 2 mg/kg/day. LOAEL - 5 mg/kg/day, ↓BW , ↓placenta wt retardation/ossification/microphthalmia
870.3700b	Prenatal Developmental Toxicity – (Rabbit)	48240226 (2009) Acceptable/guideline 0, 0.5, 1.5, 4.5 mg/kg/day	**Maternal** NOAEL – 1.5 mg/kg/day. LOAEL – 4.5 mg/kg/day, Abortions, cold ears, hind limb swelling, soft feces, ↓H2O, ↓urine, enlarged gall bladder, encrusted wounds at throat/forelimbs **Fetal** NOAEL – 1.5 mg/kg/day. LOAEL – 4.5, retarded ossification of metacarpals, phalanges, 1st cervical vertebrae
870.3800	Reproduction and Fertility Effects	48240227 (2008) 0, 0.5, 1, 3 mg/kg/day Acceptable/guideline Gavage	**Parental** NOAEL not established (M) LOAEL - 0.5 mg/kg/day ↓pituitary in F1 (15%) NOAEL - 0.5 (F) LOAEL - 1.0 mg/kg/day ↓liver weights in F0 & F1 **Reproductive** NOAEL - 3.0 mg/kg/day HDT **Offspring** NOAEL - 1.0 mg/kg/day M/F LOAEL - 3.0 mg/kg/day thinness, no milk spots, ↓BW, ↓rearing indexes with ↑deaths at PND 0-4.

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
		48240228 (1992) Acceptable/guideline 0, 1, 5, 50 ppm M: 0, 0.05, 0.23, 2.42 mg/kg/day F: 0, 0.06, 0.28, 2.92 mg/kg/day Dietary	**Parental** NOAEL = 0.23 mg/kg LOAEL = 2.42 mg/kg ↓body weight gain in P generation (males), ↓body weight and food consumption in (females) during lactation, ↑postnatal loss in all generations, ↓food consumption in P and F1 males, ↓body weight gain in male and female pups in all generations **Reproductive** NOAEL = 2.42 mg/kg HDT **Offspring** NOAEL – 0.23 mg/kg. LOAEL = 2.42 mg/kg ↓body weight and body weight gains in males and female pups, significantly different testes and ovaries weight, ↓ survival at 21 days
870.3465	Inhalation Toxicity	48240219 (1997) Acceptable/guideline 0.1, 1.4, 20.0 mg/m^3 Analytical 0.12, 1.33 and 22.4 mg/m^3	NOAEL = 0.12 mg /m^3 LOAEL = 1.33 mg /m^3 based on the results from clinical signs of toxicity battery of reflex tests and lung function measurements, hematology and clinical chemistry. bradypnea, labored breathing, red discharge or encrustations from the perinasal area. Sporadically, in females decreased motility, atony, and salivation. Signs resolved during the days of no exposure.
870.4200	Carcinogenicity - Mouse	48240223 (1999) Acceptable/guideline 0, 1,3, 15, 30 ppm M: 0, 0.12, 0.39, 1.97, 4.56 mg/kg/day F: 0, 0.15, 0.52, 2.54, 4.95 mg/kg/day	NOAEL – 0.39/0.52 (M/F) mg/kg/day LOAEL – 1.97/2.54 (M/F) mg/kg/day, ↑skin discoloration, incrustations, sores, missing/deformed ears, epidermal hyperplasia, inflammation, ulceration, M= enlarged/swollen spleens, ↑plasmacytosis mandibular LN, hematopoiesis BM, ↑reduced liver glycogen and hepatocytic atrophy (salivation seen at higher doses, 60ppm↑) There were no increased incidences of treatment related tumors compared to controls
870.4300	Combined Chronic Toxicity/ Carcinogenicity - Rat	42820221 (1999) Acceptable/guideline 0, 0.7, 2, 4 mg/kg/day	NOAEL – 0.7 mg/kg/day LOAEL – 2 mg/kg/day Severe skin lesions, enlarged LN/swollen spleens, plasmacytosis, ↑adrenal cortex vacuolation, no treatment related tumor incidence compared to controls
870.6200a	Neurotoxicity Screening Battery - Acute - Rat	48240215 (2008) Acceptable/guideline 0, **0.25, 0.50**, 1, 5, 15 mg/kg	NOAEL – 0.5 mg/kg/day in **males** LOAEL – 1.0 (M/F) mg/kg/day, ↓motor/locomotor activity, ↑staining of mouth, perianal, nose, ↑lacrimation, salivation at ↑doses
870.6200b	Neurotoxicity Screening Battery - Subchronic - Rat	48240220 (2008) Acceptable/ guideline 0,1, 2.5, 5 mg/kg/day	NOAEL – 1 mg/kg/day LOAEL – 2.6 mg/kg/day, ↓food consumption, BW/BWG males only, urine/lacrimal/perianal/oral stains, ↓figure8 maze activity (Salivation seen at higher doses)

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.6300	Neurotoxicity Developmental	48240232 (2008) Acceptable/guideline 0, 0.5, 1, 2 mg/kg/day	**Maternal** NOAEL – 1 mg/kg/day LOAEL- 2 mg/kg, BW/day for maternal animals and offspring, based on ↓body weight (-3%) and body weight gain (-9%, p<0.05), and ↓food consumption (-15%, p<0.05, in dams only). Salivation also seen. **Offspring** NOAEL – 1mg/kg/day LOAEL- 2 mg/kg, ↓ BW in M on PND 11 and 17 (- 8%, p<0.01) and in the low and high dose F on PND 11 (-6%, p<0.05) and were associated with significant reduced body weight gain that began on PND 4-11. In addition, body weight was non-statistically decreased on PND 21 in M. This difference in body weight for males persisted to study termination (statistically decreased 6-7% compared to control).
870.5100	Bacterial Reverse Mutation Test	48240233 (1993) Acceptable/guideline 0, 8, 40, 200, 1000, and 5000 µg/plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240234 (1993) Unacceptable/non-guideline 0, 7500, 10,000, 12,500, 15,000 µg/plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240235 (2006) Acceptable/guideline 0, 16, 50, 158, 500, 1581 and 5000 ug/per plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5300	In vitro mammalian cell gene mutation test	48240236 (1995) Acceptable/guideline 0, 6.25, 12.5, 25, 50, 75, and 100 µg/mL (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240237 (2007) Acceptable/guideline 0, 25, 50, or 100 µg/mL	There was no evidence of chromosomal aberrations. [Negative]
		48240239 (2007) Acceptable/guideline 0, 6, 12, 24, 48, 96 or 182 µg/mL	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5375	In vitro mammalian chromosome aberration test	48240238 (1995) Acceptable/guideline 100, 200, 500, 1000, 2500, or 5000 µg/mL (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5395	Mammalian erythrocyte micronucleus test	48240240 (2007) Acceptable/guideline 0, 125, 250, 500 mg/kg	This chemical was not found to be clastogenic or aneugenic. [Negative]

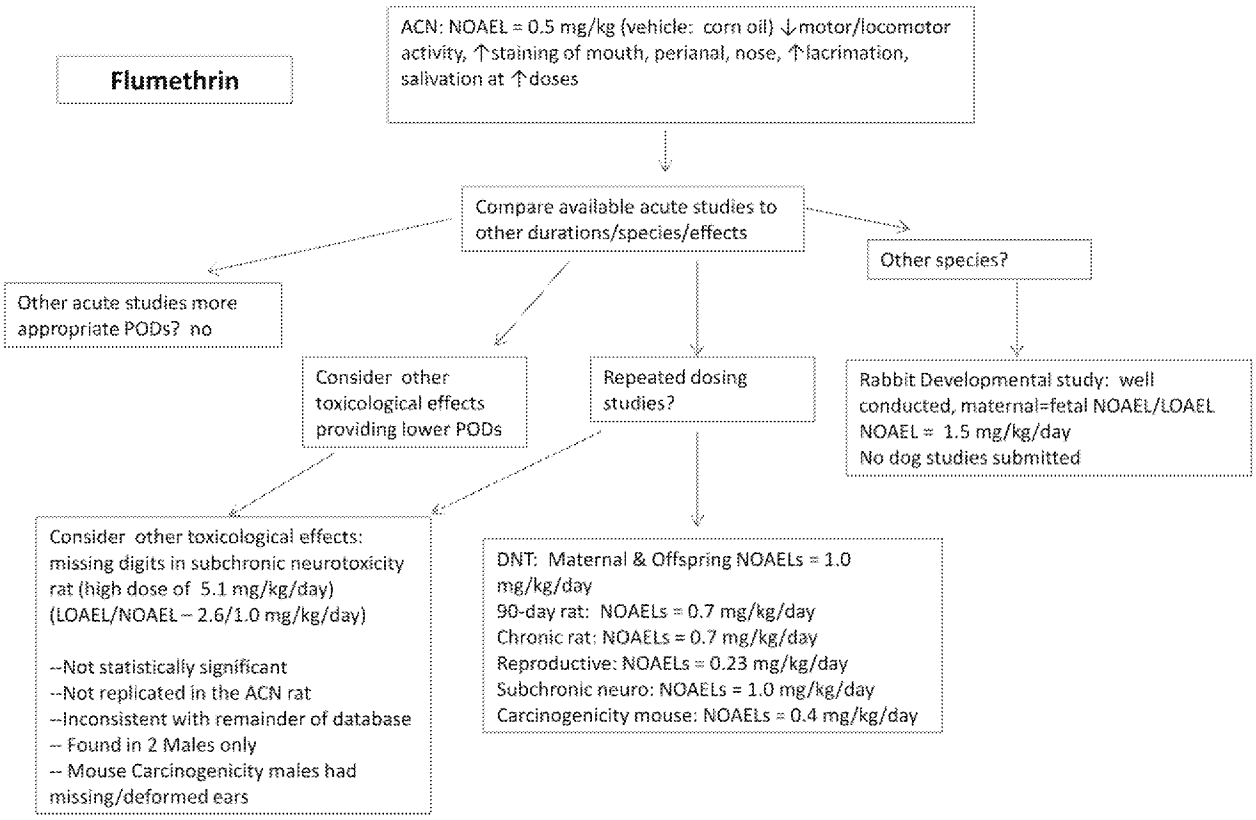
Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
		48240241 (1995) Acceptable/guideline 0, 1000mg/kg	There was no evidence of chromosomal aberrations with or without activation. [Negative]
870.5500	Unscheduled DNA Synthesis *in vitro*	48240242 (1994) Acceptable/guideline 0, 5, 10, 50, 100, 200, 300, 500 µg/mL	There was no evidence of genotoxic activity. [Negative]
870.7485	Metabolism and pharmacokinetics	48240243 (1992) Acceptable/guideline 1, 5 mg/kg	Radioactivity administered with [Cl-phenyl-U-^{14}C] flumethrin was rapidly but incompletely absorbed from the intestinal lumen of rats. Excretion of the compound was slow and mostly in the feces comprising 77-88 % of the dose. The majority of the radioactive feces eliminated had been absorbed and excreted with the bile into the gut lumen. The highest amount of radioactivity in the body was mainly found in the plasma, which at sacrifice showed the highest residue concentration in dose groups tested. All other organs exhibited significantly lower concentrations. The lowest values were determined in the brain, indicating that the blood-brain barrier is almost impermeable for the test compound and its labeled metabolites. The radioactive residues in the body excluding the gastrointestinal tract at sacrifice, seven days after dosing, were still relatively high, varying between 9 % and 20 % of the given dose. The multiple dose experiment clearly showed an accumulation of the radioactivity in the body. The 24 hour dosing interval was too short to completely allow for the elimination of the administered radioactivity. Since the renal excretion played only a negligible role, metabolite identification was conducted exclusively in the feces.
		48240244 (2000) Acceptable/non-guideline 0, 50, 160ppm	Mean plasma concentration of flumethrin and flumethrin granules after 3, 6, 13 weeks of 160ppm were bioavailability were similar
870.7800	Immunotoxicity	48240250 (2009) Acceptable/guideline 0, 10, 40, 160 ppm 0, 0.8, 3, 11.7 mg/kg/day M 0, 1, 3.5, 12.3 mg/kg/day F	Systemic NOAEL- 3/3.5 LOAEL-11.7/12.3 (M/F) ↓BW (significant in week 1 only for F)

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
Non-guideline	4-week Gavage Pilot, for 2-Gen rat repro	48240229 (2006) Acceptable/non-guideline 5.0, 7.5,10.0 mg/kg/day	Males NOAEL- Not established. LOAEL = 5 mg/kg/day (HDT) ↓reduced mean relative spleen and thymus weights and ↓absolute thymus and spleen weight. Females LOAEL - 10 mg/kg/day slightly ↓ mean body weight and reduced mean absolute and spleen weights Female NOAEL = 7.5 mg/kg/day
Non-guideline	Rat Plasma – Gavage, 2 –Gen rat repro	48240245 (2007) Acceptable/non-guideline 0, 0.5, 1.0, or 3.0 mg/kg/day	Plasma concentration study, a part of the 2-generation reproduction study no. (MRID 48240227), The animals were grouped into one control and 3 dose groups per sex and generation. All results for control group animals were below the limit of quantification. Results obtained from rats in the various dose groups showed a clear dose-concentration relation. The highest concentrations were found four hours after dosing. The concentration results for male animals were significant higher than for females.
Non-guideline	Rat Plasma – Pilot with MRID 48240230	48240231 (2006) Acceptable/non-guideline 0.08, 0.4 or 2 mg/kg/day	This study was part of an exploratory subchronic oral toxicity study (MRID 48240230) in which plasma was collected from male and female rats and analyzed to determine plasma concentrations of flumethrin. Maximum plasma levels were measured at 2 to 4 hours after administration at each dose level. At the dose concentration between 0.4 and 2.0 mg/kg there was a clear increase of plasma levels with dose that was visible in both sexes. Continuing plasma level increases were not seen in the dosage range of 3.0 to 5.0 mg/kg (after enhanced dose scheme).
Non-guideline	19-week Gavage Pilot, for 2-Gen rat repro	48240230 (2006) Acceptable/non-guideline 0, 0.08, 0.4, 2.0 mg/kg/day After day 70: 3, 4, 5 mg/kg/day	**Parental male** NOAEL- 3 mg/kg/day LOAEL - 4 mg/kg/day ↓slightly body weight. **Parental female** NOAEL - 2 mg/kg/day lack of effects prior to dose elevation LOAEL- 3 mg/kg/day ↓bw during pregnancy. **Offspring** NOAEL –2 mg/kg/day LOAEL = 3 mg/kg/day The body weight changes were insignificant for M/F. ↑absolute adrenal wt in F ($p<0.01$) and ↓thymus weight in males- 3, 4 mg/kg/day.

Appendix A.3. Hazard Identification and Endpoint Selection

mg/kg/day	SC rat	CC rat	DNT	SC mouse	CC mouse	DT rat	DT rabbit	repro/2-gen	repro/2-gen	Dermal r	SCN	ACN	Immuno
MRID	48240222	48240221	48240232	48240224	48240223	48240225	48240226	48240227 (G)	48240228 (D)	48240216	48240220	48240215	48240250
0													
0.2									NOAELp/o				
0.4					NOAEL-M							NOAEL	
0.6		NOAEL						LOAEL-M					
0.8	NOAEL-M			NOAEL-M		NOAELm		NOAELf					
1			NOAELm/o					NOAELo			NOAEL		
								LOAELf				LOAEL	
1.5				LOAEL-M			NOAELm/d						
2		LOAEL	LOAELm/o		LOAEL-M	LOAELm							
						NOAELd			NOAEL r (HDT)				
2.5									LOAEL p/o		LOAEL		
3	LOAEL-M							LOAELo					NOAEL
3.5								NOAEL r					
4													
4.5							LOAEL m/d						
5						LOAELd							
													NOAEL
10										NOAEL			LOAEL
20													
30										LOAEL			
40													
50													
80													
90													
100													
150													
200													

m = maternal; d = developmental; p = parental; o = offspring; r = reproductive; s = systemic; n = neurotoxic; f= female; M=male



A.3.1 Acute Reference Dose (aRfD) - Females age 13-49

A.3.2 Acute Reference Dose (aRfD) - General Population

Acute dietary endpoints were available to quantify risk to the general population, including infants and children. However, no PODs were chosen since the exposure scenarios did not warrant such values to be assessed.

A.3.3 Chronic Reference Dose (cRfD)

Chronic endpoints have not been chosen for flumethrin since the exposure scenarios did not warrant such values to be assessed.

A.3.4 Incidental Oral Exposure (Short-Term)

The NOAEL of 0.5 mg/kg/day from the acute neurotoxicity study is selected for this endpoint due to the overall consistency of the database and the exposure scenario of this study. The POD identified in the ACN study is found to be protective and captures the dose spread for the 2-generation reproductive study which has a lower identified NOAEL (0.23 mg/kg/day). The Hazard Identification and Endpoint Selection graph A.3 portrays the nearly flat dose-response for does which elicit many of the clinical signs seen in the database, and moreover, within these two studies. There were clear signs of increased salivation, lacrimation, and decreased motor and locomotor activity in both sexes at the LOAEL of 1.0 mg/kg /day. Therefore, the exposure scenario combined with the overlap in doses which produced an adverse effect due to treatment

within the acute neurotoxicity study gave more confidence in the data.

A.3.5 Dermal Exposure (Short-Term)

The 90-day dermal study in rats with NOAEL of 10 mg/kg/day was selected for this endpoint. The LOAEL value of 30 mg/kg/day was based on observations of clinical signs (high stepping gait), and decreased body weight and weight gain. Since a dermal toxicity study is selected for dermal risk assessment, a dermal-absorption factor is not required.

A.3.6 Inhalation Exposure (Short-Term)

An inhalation study was available to quantify risk to the general population and deemed acceptable. However, no PODs were chosen since the exposure scenarios did not warrant such values to be assessed.

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Appendix A.4. Human Equivalent (dog study vs. acute rat motor activity)

RAT (Wolansky)					DOG (Subchronic)			
chemical	rat dose (mg/kg)		human dose (mg/kg)		dog dose (mg/kg)		human dose (mg/kg)	
	BMD	**BMDL**	**BMD**	**BMDL**	**NOAEL**	**LOAEL**	**NOAEL**	**LOAEL**
beta-cyfluthrin	1.42	1.17	0.412816	0.340137	2.4	13.9	1.475491567	8.545555
bifenthrin	4.1	3.1	1.191933	0.9012176	2.2	4.2	1.352533936	2.58211
bioallethrin	65.6	42.2	19.07093	12.268189				
cyhalothrin	0.92	0.64	0.267458	0.1860578	1	2.5	0.614788153	1.53697
cyphenothrin					12.5	37.5	7.684851912	23.05456
cypermethrin	11.19	7.16	3.253105	2.081522	12.5	37.5	7.684851912	23.05456
deltamethrin	2.48	1.49	0.720974	0.4331659	1	2.5	0.614788153	1.53697
esfenvalerate	1.19	0.65	0.345951	0.188965	5	7.5	3.073940765	4.610911
fenpropathrin	6.44	5.01	1.872207	1.456484				
permethrin	63.1	44.4	18.34414	12.907762	50	500	30.73940765	307.3941
resmethrin	162.32	75.89	47.18892	22.062389				
tefluthrin	3.67	2.8	1.066925	0.814003				

Rat BW (kg) = 0.5
Dog BW (kg) = 10
Human BW (kg) = 70

Appendix B: Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. These studies, which have been utilized in the 2012 Treated Pet SOP, have been determined to require a review of their ethical conduct, have received that review, and have been determined to be ethical.

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Appendix C: Residential Exposure Algorithms and Standard Inputs

C.1. Residential Handler

Exposure Algorithms

Daily dermal and inhalation exposure (mg/day) for residential pesticide handlers, for a given formulation-application method combination, is estimated by multiplying the formula-application method-specific unit exposure by an estimate of the amount of active ingredient handled in a day, using the equation below:

$$E = UE * AR * A$$

where:

E	= exposure (mg/day);
UE	= unit exposure (mg/lb ai);
AR	= application rate (lb ai/pet); and
A	= number of animals treated per day.

Absorbed dermal and/or inhalation dose normalized to body weight is calculated as:

$$D = \frac{E * AF}{BW}$$

where:

D	= dose (mg/kg-day);
E	= exposure (mg/day);
AF	= absorption factor (dermal and/or inhalation); and
BW	= body weight (kg).

Standard Handler Algorithm Inputs

Dermal Unit Exposure Summary: No dermal exposure data are available for application of pet collars. Exposure data for spot-on applications to pets are recommended for use as surrogate data. The recommended dermal unit exposures for spot-on applications to pets or animals is based on a lognormal distribution fit with exposure monitoring data from Meo, N., et al (1997) [EPA MRID 44433303]. Meo, N., et al (1997) monitored 16 applications by commercial pet groomers to 8 dogs for approximately 14-32 minutes using a ready-to-use (RTU), disposable, snap-top, plastic-backed pipette. The dermal unit exposure is 120 mg/lb ai.

Inhalation Unit Exposure Summary: Ihalation exposure for application of pet collars is considered to be negligible.

Number of Animals Treated: It is assumed that residential handlers of pet treatment products will treat 2 animals per application (N). This estimate is based upon information available from The

Humane Society of the United States[2] which references data from the American Pet Products Manufacturers Association (APPA) 2011-2012 National Pet Owners Survey that reports pet owners have an average of 1.7 dogs and 2.2 cats.

C.2. Residential Post-application

Exposure Algorithms

Post-application Dermal Exposure Algorithm: The following method is used to calculate dermal exposures that are attributable to an adult or child contacting a treated companion pet:

$$E = TC * TR * ET$$

where:

E = exposure (mg/day);
TC = transfer coefficient (cm^2/hr);
TR = transferable residue (mg/cm^2); and
ET = exposure time (hours/day).

where:

TR = transferable residue (mg/cm^2);
AR = application rate or amount applied to animal (mg);
F_{AR} = fraction of the application rate available as transferable residue; and
SA = surface area of the pet (cm^2).

Absorbed dermal dose, normalized to body weight, is calculated as:

$$D = \frac{E * AF}{BW}$$

where:

D = dose (mg/kg-day);
E = exposure (mg/day);
AF = absorption factor (dermal); and
BW = body weight (kg).

Post-application Hand-to-Mouth Exposure Algorithm: Exposure from hand-to-mouth activity is calculated as follows (based on algorithm utilized in SHEDS-Multimedia):

[2] http://www.humanesociety.org/issues/pet_overpopulation/facts/pet_ownership_statistics.html

$$E = [HR * (F_M * SA_H) * (ET * N\_Replen) * (1- (1- SE)^{(Freq\_HtM/N\text{-}Replen)})]$$

where:

E	= exposure (mg/day);
HR	= hand residue loading (mg/cm^2);
SA_H	= surface area of one child hand (cm^2);
F_M	= fraction hand surface area mouthed /event (fraction/event);
ET	= exposure time (hr/day);
N_Replen	= number of replenishment intervals per hour (intervals/hour);
SE	= saliva extraction factor (i.e., mouthing removal efficiency); and
Freq_HtM	= number of hand-to-mouth contacts events per hour (events/hour).

and

$$HR = \frac{E * Fai_{hands}}{2 * SA_H}$$

where:

HR	= hand residue loading (mg/cm^2);
E	= dermal exposure (mg);
Fai_{hands}	= fraction of a.i. on hands compared to total residue from dermal transfer coefficient study (unitless); and
SA_H	= surface area of one child hand (cm^2).

Oral dose, normalized to body weight, is calculated as:

$$D = \frac{E}{BW}$$

where:

D	= dose (mg/kg-day);
E	= exposure (mg/day); and
BW	= body weight (kg).

Standard Post-application Algorithm Inputs

Transfer Coefficient (TC): The transfer coefficients used for pet exposure were derived from two studies representing application and grooming activities with dogs, one using a carbaryl shampoo product (Mester, 1998) and the other using a carbaryl dust product (Merricks, 1997); these are used to represent TCs for liquid and solid formulations, respectively. Data were gathered while human volunteers applied pet pesticide products to various dogs of differing sizes and fur lengths. The information identified best approximates the exposures that could occur from interactions with treated pets because these studies included the direct measurement of exposures to applicators or pet groomers. Since these individuals directly handled pesticide products and had direct contact with treated pets, it is expected that their resulting exposures are a reasonable approximation of upper bound estimates of contact with a treated animal. In the absence of direct exposure data for this scenario (e.g., homeowner activity with a treated pet), the Agency assumes that the application and grooming activities are likely to result in a protective estimate

of exposure than just the evaluation of petting, hugging or sleeping with a pet. A TC of 5,200 cm^2/hr for adults and 1,400 cm^2/hr for children is recommended for addressing all durations of post-application exposure for all liquid formulations (or formulations that behave as liquids) including RTU liquid formulations (i.e., aerosol/trigger sprays, dips, pet collars, shampoos and spot-ons).

Fraction Application Rate (F_{AR}): If chemical specific transferable residue measurements are not available, then a standard value for the fraction of active ingredient available (F_{AR}) for transfer is used. In this SOP, a screening level F_{AR} was recommended based on the review of 8 pet residue transfer, or "petting," studies (9 data sets total) submitted to the Agency. Measurements of residue transfer were derived by taking the ratio of the amount of active ingredient on a bare or gloved hand (on the day of highest observed transfer) to the amount of active ingredient applied. Five residue transfer studies were performed by means of volunteers "petting" or "stroking" animals treated with a known amount of active ingredient. Three additional residue transfer studies were conducted using a gloved mannequin hand. For each study the amount of residue transferred to the hands was determined. Based on the available pet residue transfer studies, the recommended screening level F_{AR} point estimate for use in post-application dermal exposure assessment is 0.02 (equivalent to 2%).

Exposure Time (ET): The exposure time (ET) for pets for adults and children was derived from Tsang and Klepeis, 1996 (as presented in 1997 Exposure Factors Handbook Table 15-77). Animal care is defined in the 1997 Exposure Factors Handbook as "care of household pets including activities with pets, playing with the dog, walking the dog and caring for pets of relatives, and friends." The data identified the time spent with an animal while performing household activities as recorded in 24 hour diaries by study volunteers. While the activities defined do not necessarily represent the time volunteers were actively engaged in constant contact with the animal as is implicit in the post-application dermal and incidental oral algorithms, the data are the most accurate representation of time spent with pets available and, therefore, it is assumed that contact is continual throughout the timed activity. The recommended point estimate for use in post-application dermal exposure assessments is 1.0 hour for children and 0.77 hours for adults.

Surface Area (SA): Animal surface area (SA) is determined by inputting animal weight (lbs) into an algorithm (12.3*((animal body weight (lbs)*454)^0.65)) as referenced from U.S. EPA (1993) Wildlife Exposure Factors Handbook. Representative surface areas have been calculated for the assigned cat and dog weight ranges. The surface areas for assessment are as follows:

- Cats – Small (1500 cm^2), Medium (2500 cm^2) and Large (4000 cm^2).
- Dogs – Small (3000 cm^2), Medium (7000 cm^2) and Large (11000 cm^2).

Fraction Active Ingredient on the Hands (Fai_{hands}): The fraction of active ingredient available on the hands was based on the two dermal pet transfer coefficient studies that represent application and grooming activities with dogs and used to derive dermal TCs. One study used a carbaryl shampoo product (Mester, 1998) and the other a carbaryl dust product (Merricks, 1997). These values were determined for liquid and solid formulations, respectively, by taking the average fraction of active ingredient on the hands and comparing that value to the average fraction of

active ingredient on the entire body. This analysis resulted in values of 4% for liquid formulations and 37% for solid formulations.
Fraction Hand Surface Area Mouthed (F_M): The recommended F_M value for use in post-application non-dietary ingestion exposure assessments is 0.13.

Hand Surface Area (SA_H): The hand surface area for children 1 < 2 years old of 150 cm^2, for one hand, was based on values from the Exposure Factors Handbook 2011 Edition (U.S. EPA, 2011).

Replenishment Intervals per Hour (N_Replen): This SOP assumes an estimate of 4 replenishment intervals per hour (i.e., residues on the hand will be replenished every 15 minutes). This value was selected as a conservative assumption based on the use of 30 minutes in the SHEDS model to coincide with the CHAD diaries.

Fraction of Pesticide Extracted by Saliva (SE_H): The recommended value for use in post-application non-dietary ingestion exposure assessments is 0.48.

Hand-to-Mouth Events per Hour (Freq_HtM): Frequency of hand-to-mouth events is an important variable for post-application non-dietary ingestion exposure assessments. However, there are currently no data available that specifically address the number of hand-to-mouth events that occur relative to the amount of time a child spends with a pet. As a result, the estimates for frequency of hand-to-mouth events in indoor environments from the Xue et al. (2007) meta-analysis were used as a surrogate. The indoor data were selected, even though child exposure to treated pets can occur either indoors or outdoors, because the indoor data result in a greater frequency of contacts. Therefore, using these data are the most conservative and thus the most health protective estimate of exposure. The recommended point estimate for use in post-application non-dietary exposure assessments is 20 for children 1 < 2 years old.

Appendix D: Pyrethroid Cumulative Screen

The Agency is required to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The Agency has determined that the pyrethroids and pyrethrins share a common mechanism group (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). The members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. The cumulative risk assessment (CRA) for the pyrethroids/pyrethrins was published on Nov. 9, 2011 (USEPA, 2011a) and is available at http://www.regulations.gov; EPA-HQ-OPP-2011-0746. No cumulative risk estimates of concern were identified allowing the Agency to consider new uses for pyrethroid actives. For information regarding EPA's efforts to evaluate the risk of exposure to pyrethroids, refer to http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.

As a new active ingredient, flumethrin was not included in the initial common mechanism grouping (CMG) science policy document from 2008 and was not assessed in the November 2011 pyrethroid cumulative risk assessment. However, the Agency has determined based on its chemical structure and based on the observation of neurobehavioral effects consistent with Type II pyrethroids, that flumethrin should be included in the CMG for this class of pesticides. As such, the Agency must consider the potential contribution of flumethrin to the cumulative risk assessment. As part of the assessment for the proposed flumethrin pet collar uses, the Agency has performed an analysis to determine if the use will significantly contribute to or change the overall findings in the pyrethroid CRA.

D.1. Cumulative Hazard Assessment: Relative Potency Estimation for Flumethrin

The 2011 pyrethroid CRA relies on the relative potency factor (RPF) approach using administered dose as the metric for quantifying chemical potency. In the RPF approach, the toxic potency of each chemical in the common assessment group (CAG) is determined. One member of the CAG is selected as the index chemical which is used as the point of reference for standardizing neurobehavioral potency of the other members of the CAG. In order to develop such potency estimates, EPA prefers to use a uniform measure of toxicity. In other words, the Agency prefers to use data which are from the same endpoint and same duration and to the extent possible any other factors which effect potency (e.g., time to peak effect, sex, etc).

In the pyrethroid CRA, the Agency used the two special WIL Functional Observational Battery (FOB) studies for estimating relative potency. This data was selected because these studies examined many behaviors, including key ones for evaluating neurotoxicity specific to pyrethroids. Specifically, the studies looked at a number of key parameters that are directly relevant to the Type I (e.g., hyperthermia tremors and clonus) and Type II (e.g., hypothermia, salivation, and mobility) syndromes. In addition to the WIL FOB studies, there is another study (Wolansky et al, 2006) which provides a high quality data set for estimating relative potency. Whereas the WIL FOB studies focus on endpoints specific to pyrethroid toxicity syndromes, the Wolansky study measured motor activity. Motor activity is considered an apical endpoint because it measures alterations in the activity level of an intact rat. Although the Wolansky study provides a potential data source for a uniform measure of potency, it was not utilized in the

CRA because of the lack of specific relevance to the common mechanism of action for the pyrethroids.

Although the existing toxicology database for assessment of flumethrin as a single chemical is complete with respect to the requirements for a non-food use pesticide; a specially designed FOB study is not currently available for flumethrin for use in estimating an RPF for use in the pyrethroid CRA. Flumethrin was also not one of the pyrethroids included in the Wolansky study. In lieu of this data, the Agency used the flumethrin acute neurotoxicity (ACN) study to estimate an RPF for flumethrin. In the flumethrin ACN study, effects consistent with pyrethroid toxicity syndromes (salivation and staining) are only observed at high doses and thus lack good dose response data. In contrast, motor activity shows a dose response relationship. As such, the Agency has elected to estimate the RPF for flumethrin using this motor activity data instead of the salivation data. This is not the preferred approach to estimating relative potency as motor activity does not represent the same measure of toxicity used for the other pyrethroids.

In order to estimate an RPF for flumethrin, the Agency is using the BMD for deltamethrin (i.e., the index chemical for the pyrethroids) from the Wolansky study compared with the POD from the flumethrin motor activity data. Using the deltamethrin motor activity data as the basis for estimating relative potency is preferred over the deltamethrin data from the WIL FOB as it is more appropriate to compare similar toxic effects. In other words, it is more appropriate to compare motor activity data to motor activity data than a comparison of motor activity data to FOB data. The relative potency estimates between the Wolansky and WIL FOB studies are remarkably similar (Table D.1). For the pyrethroids that have data from both studies, 8 of 11 RPFs differ by 2-fold or less.

In summary, developing an RPF in this manner is not expected to underestimate the contribution of flumethrin to the CRA as the RPFs developed using FOB data are very similar to the RPFs developed using the motor activity data for each pyrethroid. Flumethrin would be expected to have a similar RPF to the one calculated using motor activity data if a flumethrin FOB study was available. However, the Agency would prefer to use special FOB data in the relative potency determination for flumethrin . As noted in Section 2.1, the Agency encourages the development of special FOB data for flumethrin as this data would reduce the uncertainty associated with this approach.

Appendix Table D.1: Pyrethroid RPF Comparison FOB vs. Motor Activity		
Pyrethroid	FOB	Motor Activity
lambda-cyhalothrin	1.63	2.7 [a]
tefluthrin	1.36	0.68 [a]
cyfluthrin	1.15	1.75 [a]
bifenthrin	1.01	0.60 [a]
deltamethrin	1.00	1.00 [a]
fenpropathrin	0.50	0.38 [a]
metofluthrin	0.48	--
esfenvalerate	0.36	2.09 [a]
cypermethrin	0.19	0.23 [a]
tau-fluvalinate	1.00	--
cyphenothrin	0.15	--
d-allethrin	0.11	--
allethrin	0.11	0.03 [a]
prallethrin	0.10	--
permethrin	0.09	0.040 [a]
resmethrin	0.05	0.02 [a]
pyrethrins	0.02	--
imiprothrin	0.02	--
flumethrin	--	5.02 [b]

a Represents motor activity data from the Wolansky study
b Represents motor activity data from the flumethrin ACN study

D.2. Cumulative Exposure and Risk Issues

No pyrethroid pet collars were included in the 2011 pyrethroid CRA as there were no registered pet collars that contain pyrethroids at that time. The CRA did include a number of other pyrethroid pet products (e.g., spot-on, aerosol, shampoo, and trigger pump sprayer formulations). In order to determine if the proposed flumethrin pet collar will significantly contribute to or change the overall findings in the pyrethroid CRA the Agency performed a quantitative exposure and risk assessment. This assessment used the flumethrin RPF discussed above in Section D.1 as well as the same exposure algorithms and inputs that were used in the 2011 pyrethroid CRA.

The MOEs calculated and presented in Appendix Table D.2 were compared with the MOEs currently driving pet exposure and risk estimates in Table 6.4.7a from the 2011 pyrethroid CRA. Dermal adult pet handler exposure and risk estimates are currently driven by the permethrin pet shampoo use pattern with a dermal MOE of 27,000 which is lower than the estimated MOE for flumethrin (190,000). Dermal adult and 1 < 2 year old pet post-application exposure and risk estimates are currently driven by the cyphenothrin spot-on use pattern with adult and 1 < 2 year old dermal MOEs of 9,800 and 4,200, respectively, both of which are lower than the estimated MOEs for flumethrin (33,000 and 14,000, respectively). For 1 < 2 year olds, hand-to-mouth pet post-application exposure and risk estimates are currently driven by the cyphenothrin spot-on use pattern with an MOE of 22,000, which is lower than the estimated MOE for flumethrin (72,000). A summary of these MOEs is presented in Appendix Table D.2 while the detailed calculations are presented in Appendix Table D.3. In all cases, the estimated flumethrin MOEs using the RPF method were higher (i.e., less of a risk concern) than those used in the 2011 pyrethroid CRA. Thus the Agency has determined that the proposed flumethrin pet collar use will not significantly contribute to or change the overall findings in the 2011 pyrethroid CRA.

Appendix Table D.2: Comparison of Flumethrin MOEs with Pyrethroid Cumulative MOEs

Chemical		Scenario	Route	Population	MOE
New Use	Flumethrin	Pet collar	Handler dermal	Adult	190,000
			Postapp dermal	Adult	33,000
				Children (1 < 2 yr old)	14,000
			Postapp Hand-to-Mouth	Children (1 < 2 yr old)	72,000
CRA	Permethrin	Pet shampoo	Handler dermal	Adult	27,000
	Cyphenothrin	Pet spot-on	Postapp dermal	Adult	9,800
				Children (1 < 2 yr old)	4,200
			Postapp Hand-to-Mouth	Children (1 < 2 yr old)	22,000

Appendix Table D.3: Flumethrin Screening Level "Cumulative" MOEs

Pet Handler Exposure

Exposure Scenario	Application Rate (mg ai/dog)	Amount Treated Daily (animals)	Baseline Dermal Unit Exposure (mg/lb ai)	Baseline Inhalation Unit Exposure (mg/lb ai)	Baseline Dermal Unit Exposure (mg/lb ai)	Baseline Inhalation Unit Exposure (mg/lb ai)	Baseline Dermal Dose	Adjusted Baseline Dermal Dose (mg/kg/day) [a]	Adjusted Baseline Dermal MOE [b]	Baseline Inhalation Dose	Adjusted Baseline Inhalation Dose (mg/kg/day)	Baseline Inhalation MOE
Pet Dermal (adults)	16.7	2	220	NA	220	N/A [b]	0.0000113	0.000057	190,000	N/A [b]		

Pet Post-application Hand-to-Mouth Exposure

Exposure Scenario	Fai_{hands}	1-2 yr old Dermal Exposure	SA_H (cm2)	HR_f (mg/cm2)	F_M Fraction of Hand Surface Area Mouthed / Event	Exposure Time (hours/day)	N_Replen Number of replenishment intervals per hr (intervals/hr)	SE Extraction by Saliva	Freq_HtM H-t-M events per hour	BW	Average Daily Dose (mg/kg/day)	Adjusted Dose (mg/kg/day) [a]	Adjusted MOE [b]
Hand to Mouth (1 < 2 year olds)	0.039	0.03401	150	4.4214E-06	0.13	0.99	4	0.5	20	11.4	0.0000290	0.000145646	72,000

Pet Post-application Dermal Exposure

Exposure Scenario	Application Rate (mg ai/dog)	Body Weight (kg)	Fraction of App Rate Available	Surface Area of Medium Dog (cm2/animal)	Transferable Residue	Transfer Coefficient (cm2/hr)	Exposure Time (hours)	Absorbed Dermal Dose (mg/kg/day)	Adjusted Dose (mg/kg/day) [a]	Adjusted MOE [b]
Pet Dermal (1 < 2 year olds)	16.7	11.4	0.00960	7000	0.00002	1,500	0.99	0.00014917	0.00074883	14,000
Pet Dermal (adults)	16.7	71.8	0.00960	7000	0.00002	5,200	0.77	6.38601E-05	0.00032058	33,000

a Doses were adjusted based on an estimated flumethrin RPF of 5.02
b MOEs were calculated by comparing the adjusted dose to the oral BMD_{20} from the WIL FOB data for the index chemical, deltamethrin (14.5 mg/kg/day)
c Handler inhalation exposure is expected to be negligible from flumethrin pet collars and thus a quantitative assessment was not performed.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

February 1, 2012

MEMORANDUM: Acute Toxicity Study and Waiver Request DERs for 11556-RLL

Subject:	Name of Pesticide Product:	PNR1427 INSECTICIDE COLLAR
	EPA Reg. No. /File Symbol:	11556-RLL
	DP Barcode:	DP 385538
	Decision No.:	440307
	Action Code:	R110.0
	PC Codes:	129099 (Imidacloprid
		036007 (Flumethrin: 96.2%)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
Feb. 1, 2012

E. McLendon
Feb. 1, 2012

To: BeWanda Alexander/Richard Gebken RM 10
Insecticide Branch
Registration Division (7505P)

Registrant: BAYER HEALTHCARE LLC

FORMULATION FROM LABEL:

Active Ingredient(s):		by wt.
036007 Flumethrin*		4.5%
129099 Imidacloprid		10.0%
Other Ingredient(s):		85.5%
	TOTAL	100.0%

*Trans Z-1/trans Z-2 ratio: max 66% trans Z-1 and min 34% trans Z-2

ACTION REQUESTED: The Risk Manager requests:

"Please review attached acute toxicity studies submitted in support of a new end use product containing two active ingredients: one currently registered (imidacloprid) and a new active ingredient (flumethrin)."

ED_005739A_00099538-00001

BACKGROUND:

The material received for review includes waiver requests for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, and primary eye irritation (MRIDs 48240102 through 48240105), as well as a primary dermal irritation study (in MRID 48240106) and a dermal sensitization study (MRID 48240107). This product is a collar (PNR1427 Insecticide, with an ingredient statement indicating that it contains 4.5% flumethrin and 10.0% imidacloprid); both ingredients are embedded in a plastic matrix.

COMMENTS AND RECOMMENDATIONS:

1. It is noted by TRB that although Imidacloprid-containing formulations have been registered as cat and dog spot-ons, no Imidacloprid-containing collars have been registered, so this collar represents both a new use for Imidacloprid and a new active ingredient in Flumethrin.

2. A contractor (Summitec Corporation) did the primary reviews on the waiver requests and acute toxicity studies, producing a DER for each; TRB did secondary reviews on the DERs, making revisions where appropriate.

3. TRB concludes that, based on the nature of this product (a plastic collar for use on dogs and/or cats) and the relatively low release rates of the two active ingredients from the collar matrix, waivers are appropriate for the oral toxicity, dermal toxicity, inhalation toxicity and eye irritation studies. The remaining two reports (primary dermal irritation study in MRID 48240106 and dermal sensitization study in 48240107) have been classified as acceptable.

4. The following is the acute toxicity profile for EPA File Symbol 11556-RLL (PNR1427 INSECTICIDE COLLAR), based on the considerations indicated above:

Acute oral toxicity	IV	Waived	MRID 48240102
Acute dermal toxicity	IV	Waived	MRID 48240103
Acute inhalation toxicity	IV	Waived	MRID 48240104
Primary eye irritation	IV	Waived	MRID 48240105
Primary dermal irritation	IV	Acceptable	MRID 48240106
Dermal sensitization	Not a sensitizer	Acceptable	MRID 48240107

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5. Based on the acute toxicity profile above, and taking into consideration the proposed uses specified on the label, information in the CSF, and declaration of ingredients on the proposed label, the following would be the precautionary and first aid labeling for EPA File Symbol 11556-RLL as obtained from the Label Review System:

PRODUCT ID #: **011556-00155**

PRODUCT NAME: **PNR1427 INSECTICIDE**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **CAUTION**

Hazards to Humans:

[The registrant has proposed the following: "Do not open package until ready to use. Do not allow children to play with the collar [or reflectors]. Avoid contact with eyes, skin or clothing. Wash thoroughly with soap and cold water after fitting the collar. People with sensitivity reactions to the ingredients of the collar should avoid contact with the collar. [Choking hazard. Contains small parts]. Do not place collar [or reflectors] in mouth. Not intended for use on humans." These statements are acceptable.]

Hazards to Domestic Animals:

[The statements proposed by the registrant are acceptable (refer to http://www.epa.gov/PR_Notices/pr96-6.html). It is noted that the minimum ages (not to be used on puppies under seven weeks of age or kittens under ten weeks of age) are supported by the puppy and kitten studies in MRIDs 48240110 and 48240111, respectively (refer to the TRB review for 11556-155 dated January 27, 2012).

First Aid:

[No statements required; registrant has the option of using Toxicity Category III statements].

6. The CSF (dated 8/25/2010) for EPA File Symbol 11556-RLL should also be reviewed and accepted by the TRB Chemistry Team.

DATA EVALUATION RECORD

CYCLOPROPANECARBOXYLIC ACID
[PNR 1427]

STUDY TYPE: ACUTE ORAL TOXICITY - RAT [OPPTS 870.1100; OECD 425]
ACUTE DERMAL TOXICITY - RAT [OPPTS 870.1200; OECD 402]
ACUTE INHALATION TOXICITY - RAT [OPPTS 870.1300; OECD 403]
ACUTE EYE IRRITATION - RABBIT [OPPTS 870.2400; OECD 405]
ACUTE DERMAL IRRITATION - RABBIT [OPPTS 870.2500; OECD 404]
DERMAL SENSITIZATION - GUINEA PIG [OPPTS 870.2600; OECD 406]
MRID: 48240102, 48240103, 48240104, 48240105, 48240106, and 48240107

Prepared for
Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Summitec Corporation
9724 Kingston Pike, Suite 602
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Task Order No. 3-B-37

Primary Reviewer:
Donna L. Fefee, D.V.M.

Signature: Donna L. Fefee
Date: JUL 15 2011

Secondary Reviewers:
Thomas C. Marshall, Ph.D., D.A.B.T.

Signature: Thomas C Marshall
Date: JUL 15 2011

Robert H. Ross, M.S., Program Manager

Signature: Robert H. Ross
Date: JUL 15 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: Jennifer Goldberg
Date: JUL 15 2011

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

EPA Reviewer: **Byron T. Backus, Ph.D.** **Date:** January 31, 2012
Risk Manager (EPA): 10

STUDY TYPE: Acute Oral Toxicity - Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL: PNR1427 Insecticide (Imidacloprid [10% w/w] + Flumethrin [4.5% w/w]); solid collar.

CITATION: Chopade, H. (2010) Request for waiver from the requirement of acute oral toxicity study - PNR1427 Insecticide. Study Number 33854. Unpublished study prepared by Bayer Healthcare LLC, Animal Health Division, Shawnee Mission, Kansas. August 31, 2010. MRID 48240102.

SPONSOR: Bayer Healthcare LLC, Animal Health Division, 12707 W. 63rd Street, Shawnee Mission, Kansas

EXECUTIVE SUMMARY: Bayer Healthcare LLC, Animal Health Division requests a waiver from the requirement for an acute oral toxicity study (OPPTS 870.1100; OECD 425). The request is based on the following:

The formulation is a solid that contains highly hydrophobic inert ingredients along with active ingredients that have low water solubilities. The study author states that it is therefore impractical to obtain a solution or suspension of the formulation in water, corn oil, or other vehicles commonly used for dosing solids in an acute toxicity study.

According to the study author, U.S. EPA representatives (B. Backus and B. Alexander) considered this waiver request to be reasonable but requested that Bayer Healthcare LLC, Animal Health Division include information on the release rate of the active ingredients from the collar in the justification for the waiver.

Release rates of active ingredients are given in the following representative Companion Animal Safety Studies:

MRIDs 4824018 + 48674702 (61-day study with adult cats; refer to DP 385560 + DP 396978): One collar group: 347.82 mg Imidacloprid and 98.72 mg Flumethrin (equals dosage rates of 89.93 mg Imidacloprid/kg and 25.15 mg Flumethrin/kg or 1.474 mg Imidacloprid/kg/day and 0.412 mg Flumethrin/kg/day).

MRIDs 48240109 + 48674701 (61-day study with adult cats; refer to DP 385560 + DP 396978): One collar group: 971.79 mg Imidacloprid and 224.93 mg Flumethrin (equals dosage rates of 83.42 Imidacloprid/kg and 19.09 mg Flumethrin/kg or 1.368 mg Imidacloprid/kg/day and 0.313 mg Flumethrin/kg/day).

MRID 48240110 (180-day study with puppies; collars were replaced on days 29, 90, 125, and 148; refer to DP 385560 + DP 396978): One collar group: 219.14 mg Imidacloprid and 51.74 mg Flumethrin in the period from Days 0 to 29 (equals dosage rates of 76.98 mg Imidacloprid and 18.69 mg Flumethrin/kg or 2.654 mg Imidacloprid/kg/day and 0.644 mg Flumethrin/kg/day).

MRID 48240111 (180-day study with kittens; collars were replaced on days 29, 90, 125 and 149; refer to DP 385560 + DP 396978): One collar group: 182.81 mg Imidacloprid and 12.69 mg Flumethrin in the period from Days 0 to 29 (equals dosage rates of 123.42 mg Imidacloprid/kg and 8.51 mg Flumethrin/kg or 4.256 mg Imidacloprid/kg/day and 0.293 mg Flumethrin/kg/day).

The label for PNR1427 Insecticide indicates the Flumethrin Trans Z-1/trans Z-2 ratio: max 66% trans Z-1 and min 34% trans Z-2. From MEID 48240203 the rat oral LD50 value for Flumethrin technical (59.9% trans-Z1-isomer and 40.1% trans-Z2- isomer) is 175 mg/kg (1/3 rats dosed at this level died) with a 95% P.L. confidence limit of 42.89 to 104 mg/kg. The dosage rates given above range from 0.293 to 0.644 mg Flumethrin/kg/day; the 0.644 mg corresponds to a cumulative dosage of 18.69 mg/kg given over a 29-day period, or 10.7% of the 175 mg/kg for a single dose LD50.

The LD50 for technical (75%) Imidacloprid is 424 mg/kg for male rats and 450-475 mg/kg for females (refer to MRID 42055331, TXR 0011070). The maximum cumulative dosage in the 61-day studies was 89.93 mg Imidacloprid/kg, or 21.2% of the 424 mg/kg for a single dose LD50.

The following is from a TRB review dated December 29, 2011 for 11556-RLL (DP 392118; TXR 5013553):

The dosage rates from a ~10 g cat collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (28-91 day) Cat & Kitten Studies: Imidacloprid: Mean dosage rate = 1.88 mg/kg/day (range: 0.71-3.72 mg/kg/day). Flumethrin: Mean dosage rate = 0.19 mg/kg/day (range: 0.05-0.44 mg/kg/day).

Long-term (238-245 day) Cat Studies: Imidacloprid: Mean dosage rate = 0.46 mg/kg/day (range: 0.33-0.60 mg/kg/day). Flumethrin: Mean dosage rate = 0.088 mg/kg/day (range: 0.06-0.12 mg/kg/day).

The dosage rates from a ~35 g dog collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (23-91 day) Dog & Puppy Studies: Imidacloprid: Mean dosage rate = 1.49 mg/kg/day (range: 0.70-2.44 mg/kg/day). Flumethrin: Mean dosage rate = 0.24 mg/kg/day (range: 0.07-0.42 mg/kg/day).

Long-term (238-245 day) Dog Studies: Imidacloprid: Mean dosage rate = 0.42 mg/kg/day (range: 0.33-0.52 mg/kg/day). Flumethrin: Mean dosage rate = 0.12 mg/kg/day (range: 0.09-0.18 mg/kg/day).

Based on the relatively low rates of release of these actives (and particularly the very slow release of flumethrin), TRB concludes that the acute oral LD50 toxicity study for this collar can be waived, and that it can be assigned to EPA Toxicity Category IV by this exposure route.

COMPLIANCE: Signed and dated GLP and Data Confidentiality statements were provided.

EPA Reviewer: **Byron T. Backus, Ph.D.** **Date:** January 31, 2012
Risk Manager (EPA): 10

STUDY TYPE: Acute Dermal Toxicity - Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: PNR1427 Insecticide (Imidacloprid [10% w/w] + Flumethrin [4.5% w/w]); solid collar.

CITATION: Chopade, H. (2010) Request for waiver from the requirement of acute dermal toxicity. Study Number 33855. Unpublished study prepared by Bayer HealthCare LLC, Animal Health Division, Shawnee Mission, Kansas. August 31, 2010. MRID 48240103.

SPONSOR: Bayer Healthcare LLC, Animal Health Division, 12707 W. 63rd Street, Shawnee Mission, Kansas

EXECUTIVE SUMMARY: Bayer Healthcare LLC, Animal Health Division requests a waiver from the requirement for an acute dermal toxicity study (OPPTS 870.1200; OECD 402). The request is based on the following:

The formulation is a solid that contains highly hydrophobic inert ingredients along with active ingredients that have low water solubilities. This, along with the fact that it is difficult to pulverize the collar into a fine powder, would make it difficult to properly moisten the ground material with a suitable vehicle in order to maintain the contact with the test animals' skin.

The same rate of release arguments for the active ingredients considered in the oral LD50 waiver can also be applied to this situation.

Based on the relatively low rates of release of these actives (and particularly the very slow release of flumethrin), TRB concludes that the acute dermal LD50 toxicity study for this collar can be waived, and that it can be assigned to EPA Toxicity Category IV by this exposure route.

COMPLIANCE: Signed and dated GLP and Data Confidentiality statements were provided.

ED_005739A_00099538-00007

EPA Reviewer: **Byron T. Backus, Ph.D.** **Date:** January 31, 2012
Risk Manager (EPA): 10

STUDY TYPE: Acute Inhalation Toxicity - Rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: PNR1427 Insecticide (Imidacloprid [10% w/w] + Flumethrin [4.5% w/w]); solid collar.

CITATION: Chopade, H. (2010) Request for waiver from the requirement of acute inhalation toxicity study - PNR1427 Insecticide. Study Number 33856. Unpublished study prepared by Bayer HealthCare LLC, Animal Health Division, Shawnee Mission, Kansas. August 31, 2010. MRID 48240104.

SPONSOR: Bayer Healthcare LLC, Animal Health Division, 12707 W. 63rd Street, Shawnee Mission, Kansas

EXECUTIVE SUMMARY: Bayer Healthcare LLC, Animal Health Division requests a waiver from the requirement for an acute inhalation toxicity study (OPPTS 870.1300; OECD 403). The request is based on the following:

The end use formulation is a solid plastic that is difficult to pulverize into a fine powder, and it also is not volatile. It was not possible to grind the material finely enough or suspend the material in the air.

The reviewer agrees that non-volatile products that cannot be readily aerosolized (e.g. plastic, viscous liquids, waxes, and resins) and that are not heated or diluted to an inhalable state during use or application are appropriate candidates for an inhalation waiver.

The reviewer recommends that this waiver be granted.

COMPLIANCE: Signed and dated GLP and Data Confidentiality statements were provided.

ED_005739A_00099538-00008

EPA Reviewer: **Byron T. Backus, Ph.D.** **Date:** February 1, 2012
Risk Manager (EPA): 10

STUDY TYPE: Primary Eye Irritation - Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: PNR1427 Insecticide (Imidacloprid [10% w/w] + Flumethrin [4.5% w/w]); solid collar.

CITATION: Chopade, H. (2010) Request for waiver from the requirement of acute eye irritation toxicity study - PNR1427 Insecticide. Unpublished study prepared by Bayer HealthCare LLC, Animal Health Division, Shawnee Mission, Kansas. August 31, 2010. MRID 48240105.

SPONSOR: Bayer Healthcare LLC, Animal Health Division, 12707 W. 63rd Street, Shawnee Mission, Kansas

EXECUTIVE SUMMARY: Bayer Healthcare LLC, Animal Health Division requests a waiver from the requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405). The request is based on the following:

The formulation is a solid that is difficult to pulverize into a fine powder. It also contains highly hydrophobic inert ingredients along with active ingredients that have low water solubilities. These properties would make it difficult to dissolve or suspend the coarsely pulverized material in a suitable vehicle and accurately measure 100 mg or 0.1 mL.

The Agency recommended use of a cryogenic grinding method for one of the TGAI (Flumethrin). The results of this study (from MRID 48240211 the technical Flumethrin remained a powder at low temperature, but reverted to a glassy substance when brought to room temperature; see TRB review TXR 5013525 dated December 6, 2011) indicated that it was impractical to use this methodology to conduct an eye irritation study.

A primary eye irritation study (in MRID 42055334) conducted on technical (75%) Imidacloprid (refer to TXR 0011070) demonstrated it is in EPA Toxicity Category IV by this exposure route.

In addition, this formulation is a plastic collar, and the actives are embedded in and released only slowly from the matrix.

Based on the above considerations, TRB concludes that a waiver for the eye irritation study is appropriate. The formulation (a dog or cat collar) can be assigned to EPA Toxicity Category IV by this exposure route.

COMPLIANCE: Signed and dated GLP and Data Confidentiality statements were provided.

EPA Reviewer: **Byron T. Backus, Ph.D.** **Date:** January 30, 2012
Risk Manager (EPA): 10

STUDY TYPE: Primary Dermal Irritation - Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: PNR 1427; 9.96% Imidacloprid, 4.35% Flumethrin; Lot No.: KP05KF6; EPSL Reference No.: 090626-2R; Gray solid collar; pH: not available; expiration date: December 1, 2009; stored at room temperature; found to be stable for the duration of testing.

CITATION: Durando, J. (2009) PNR 1427: primary skin irritation study in rabbits. Study Number 27805. Unpublished study prepared by Eurofins | Product Safety Laboratories, Dayton, New Jersey. September 30, 2009. MRID 48240106.

SPONSOR: Bayer Healthcare LLC, Animal Health Division, 12707 W. 63rd Street, Shawnee, Kansas

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 48240106), two male and one female, young adult, New Zealand albino rabbits were dermally exposed for 4 hours to 1"x1" pieces of PNR 1427 (9.96% Imidacloprid, 4.35% Flumethrin; Lot #KP05KF6) moistened with 0.1 mL of distilled water. The doses were applied to intact, clipped, 6-cm^2 application sites on the trunk and covered by a 4-ply gauze pad secured with semi-occlusive 3-inch Micropore tape wrapped around the trunk. The animals were observed at 30-60 minutes and 24, 48, and 72 hours after patch removal, and any irritation at the dose sites was scored according to Draize. The animals were supplied by Robinson Services Inc., Clemmons, North Carolina; the body weights and exact ages of the animals were not provided.

There were no observations of edema. At 30-60 minutes after patch removal, all treated sites exhibited very slight erythema (score=1). At 24 hours, very slight erythema remained present on one site but had resolved on the other two sites. At 48 and 72 hours, all sites were clear of erythema, edema, and/or other changes to the skin. No abnormal systemic clinical signs were reported.

In this study, the primary Irritation Index (PII) is 0.33, and the formulation is a slight irritant. PNR 1427 is classified as EPA Toxicity Category IV for primary dermal irritation.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary skin irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

ED_005739A_00099538-00010

RESULTS and DISCUSSION:

INDIVIDUAL SKIN IRRITATION SCORES [ERYTHEMA/EDEMA]

Animal No.	Sex	Hours after patch removal			
		1	24	48	72
3501	M	1/0	0/0	0/0	0/0
3502	M	1/0	0/0	0/0	0/0
3503	F	1/0	1/0	0/0	0/0
Severity of Irritation - Mean Score		1.00/0.00	0.33/0.00	0.00/0.00	0.00/0.00

A. Observations: There were no observations of edema. At 30-60 minutes after patch removal, all treated sites exhibited very slight erythema (score=1). At 24 hours, very slight erythema remained present on one site but had resolved on the other two sites. At 48 and 72 hours, all sites were clear of erythema, edema, and/or other changes to the skin. No abnormal systemic clinical signs were reported.

B. Results: The PDII is 0.33.

C. Reviewer's Conclusions: In agreement with the study author, the test material is a slight irritant. The test material is classified as EPA Toxicity Category IV.

D. Deficiencies: As a minor deficiency, the ages of the animals were not provided.

ED_005739A_00099538-00011

EPA Reviewer: **Byron T. Backus, Ph.D.** **Date:** January 30, 2012
Risk Manager (EPA): 10

STUDY TYPE: Dermal Sensitization – Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: PNR 1427; 9.96% Imidacloprid, 4.35% Flumethrin; Lot No.: KP05KF6; EPSL Reference No.: 090626-2R; Gray solid collar; pH: not available; expiration date: December 1, 2009; stored at room temperature; found to be stable for the duration of testing.

CITATION: Durando, J. (2009) PNR 1427: dermal sensitization study in guinea pigs (Buehler method). Study Number 27806. Unpublished study prepared by Eurofins | Product Safety Laboratories, Dayton, New Jersey. October 12, 2009. MRID 48240107.

SPONSOR: Bayer Healthcare LLC, Animal Health Division, 12707 W. 63rd Street, Shawnee, Kansas

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 48240107), twenty young adult, male, Hartley albino guinea pigs were tested with PNR 1427 (9.96% Imidacloprid, 4.35% Flumethrin; Lot #KP05KF6) using the Buehler method. For induction and challenge the test material was applied as a 20-22 mm circle (cut from the solid material), moistened with 0.1 mL of distilled water and held in place with non-allergenic Durapore adhesive tape. A separate naïve control group of ten males was treated during challenge only. The animals were supplied by Elm Hill Breeding Labs, Chelmsford, Massachusetts and weighed 302-400 g; exact ages of the animals were not reported.

No positive dermal reactions were seen following challenge. No abnormal systemic clinical signs were reported, and all of the animals gained weight over the course of the study.

Based on this study, PNR 1427 is *not* a dermal sensitizer.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal sensitization study (OPPTS 870.2600; OECD 406) in the Guinea pig.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. PROCEDURE

A. Induction: The dorsal area and flanks of the animals were clipped one day prior to each treatment. For each of three successive weekly inductions, a 20-22 mm circle (cut from the solid test material) moistened with 0.1 mL of distilled water was applied to the left side of each animal and secured in place with adhesive tape wrappings for six hours. Reactions were scored 24 and 48 hours post application.

B. Challenge: Twenty-seven days after the first induction, the test animals were challenged with a 20-22 mm circle (cut from the solid test material) moistened with 0.1 mL of distilled water, applied to naive sites on the right side of each animal for 6 hours using the same procedure as described for induction. Reactions were scored 24 and 48 hours post application.

C. Naive Controls: At challenge, a separate "naive" group of ten previously untreated animals was also treated with a 20-22 mm circle (cut from the solid test material) moistened with 0.1 mL of distilled water. Reactions were scored 24 and 48 hours post application.

II. RESULTS and DISCUSSION:

A. Reactions and duration: No erythema was seen at any dose site, following induction or challenge.

B. Positive control: The study report included the results from a positive control study with alpha-Hexylcinnamaldehyde (EPSL Study #27592, completed on June 26, 2009). The positive control study was conducted within six months of the submitted study, and the study author stated that the induction and challenge procedures used in both studies were similar. The reviewer considers the results to be appropriate.

C. Reviewer's Conclusions: In agreement with the study author, the test material is *not* a dermal sensitizer.

D. Deficiencies: According to minutes taken during a teleconference between representatives of Bayer Healthcare LLC, Animal Health Division and representatives of the U.S. EPA (provided in MRIDs 48240102, 48240103, 48240104, 48240105), a U.S. EPA respresentative requested that a dermal sensitization be conducted using ground collar material. The current study instead used cut pieces of the collar with no explanation provided. As a minor deficiency, the ages of the animals were not provided.

ACUTE TOX ONE-LINERS:

1. DP BARCODE: 385538				
2. PC CODES: 129099, 036007				
3. CURRENT DATE: February 1, 2012				
4. TEST MATERIAL: PNR 1427 (9.96% Imidacloprid, 4.35% Flumethrin; Lot #KP05KF6)				
Study/Species/Lab Study # /Date	**MRID**	**Results**	**Tox. Cat.**	**Core Grade**
Acute oral toxicity / rat Bayer HealthCare LLC, Animal Health Division Study #33854 / August 31, 2010	48240102	Waiver Recommended	IV	W
Acute dermal toxicity / rat Bayer HealthCare LLC, Animal Health Division Study #33855 / August 31, 2010	48240103	Waiver Recommended	IV	W
Acute inhalation toxicity / rat Bayer HealthCare LLC, Animal Health Division Study #33856 / August 31, 2010	48240104	Waiver Recommended ·	IV	W
Primary eye irritation / rabbit Bayer HealthCare LLC, Animal Health Division Study #33857 / August 31, 2010	48240105	Waiver Recommended.	IV	W
Primary dermal irritation /rabbit Eurofins | Product Safety Laboratories Study #27805 / September 30, 2009	48240106	Slight irritant; PII=0.33	IV	A
Dermal Sensitization /guinea pig Eurofins | Product Safety Laboratories Study #27806 / October 12, 2009	48240107	*Not* a sensitizer	--	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

December 29, 2011

MEMORANDUM: IMIDACLOPRID 10%/FLUMETHRIN 4.5% DOG & CAT COLLARS: DOSAGE AND RELEASE RATES OF ACTIVES

Subject:	Name of Pesticide Product:	PNR1427 INSECTICIDE
	EPA Reg. No. /File Symbol:	11556-RLL
	DP Barcode:	DP 392118
	Decision No.:	440307
	Action Code:	R110.0
	PC Code:	036007 (Flumethrin: 4.5%)
		129099 (Imidacloprid: 10.0%)

Byron T. Backus
12/29/2011
MHaskus, Ph.D.

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

To: BeWanda Alexander/Richard Gebken RM 10
Insecticide Branch
Registration Division (7505P)

Registrant: BAYER HEALTHCARE LLC

FORMULATION FROM LABEL:

Active Ingredient(s):		by wt.
036007 Flumethrin		4.5%
129099 Imidacloprid		10.0%
Other Ingredient(s):		85.5%
	TOTAL	100.0%

ED_005739A_00099540-00001

Action Requested: The Risk Manager requests a review of MRID 482401-40, a 117-page document summarizing dosages and release rates of imidacloprid and flumethrin from a number of cat and dog collar studies.

COMMENTS AND RECOMMENDATIONS:

The following is the executive summary for the review compilation in MRID 48240140:

The material in MRID 48240140 represents the compilation of release rates in a series of studies of the two active ingredients from cat and dog collars containing ~10% Imidacloprid and ~4.5% Flumethrin. Collars were weighed, then worn by cats or dogs for varying periods of time, after which they were weighed and analyzed for content of the two active ingredients.

The dosage rates from a ~10 g cat collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (28-91 day) Cat & Kitten Studies: Imidacloprid: Mean dosage rate = 1.88 mg/kg/day (range: 0.71-3.72 mg/kg/day). Flumethrin: Mean dosage rate = 0.19 mg/kg/day (range: 0.05-0.44 mg/kg/day).

Long-term (238-245 day) Cat Studies: Imidacloprid: Mean dosage rate = 0.46 mg/kg/day (range: 0.33-0.60 mg/kg/day). Flumethrin: Mean dosage rate = 0.088 mg/kg/day (range: 0.06-0.12 mg/kg/day).

The dosage rates from a ~35 g dog collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (23-91 day) Dog & Puppy Studies: Imidacloprid: Mean dosage rate = 1.49 mg/kg/day (range: 0.70-2.44 mg/kg/day). Flumethrin: Mean dosage rate = 0.24 mg/kg/day (range: 0.07-0.42 mg/kg/day).

Long-term (238-245 day) Dog Studies: Imidacloprid: Mean dosage rate = 0.42 mg/kg/day (range: 0.33-0.52 mg/kg/day). Flumethrin: Mean dosage rate = 0.12 mg/kg/day (range: 0.09-0.18 mg/kg/day).

This report is classified as acceptable (Non-Guideline). It provides useful information regarding the rates of release of the two active ingredients from a collar containing ~10% Imidacloprid and ~4.5% Flumethrin and the exposure to cats and dogs wearing this collar.

Reviewer: Byron T. Backus, Ph.D. **Date:** December 29, 2011
Risk Manager (EPA): 10

STUDY TYPE: Active Release Rates from Cat & Dog Collars (Non-Guideline)

TEST MATERIAL: Collars containing ~10% Imidacloprid and ~4.5% Flumethrin

CITATION: Stanneck, D. (2010) Dosage of the Imidacloprid 10% Flumethrin 4.5% Collar and Release of the Active Ingredients over Time in Cats and Dogs: Review Compilation. Project Number: 35992, PNR1427. Unpublished study prepared by Bayer HealthCare, LLC. 120 p. June 28, 2010. MRID 48240140.

SPONSOR: Bayer HealthCare, LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

EXECUTIVE SUMMARY:

The material in MRID 48240140 represents the compilation of release rates in a series of studies of the two active ingredients from cat and dog collars containing ~10% Imidacloprid and ~4.5% Flumethrin. Collars were weighed, then worn by cats or dogs for varying periods of time, after which they were weighed and analyzed for content of the two active ingredients.

The dosage rates from a ~10 g cat collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (28-91 day) Cat & Kitten Studies: Imidacloprid: Mean dosage rate = 1.88 mg/kg/day (range: 0.71-3.72 mg/kg/day). Flumethrin: Mean dosage rate = 0.19 mg/kg/day (range: 0.05-0.44 mg/kg/day).

Long-term (238-245 day) Cat Studies: Imidacloprid: Mean dosage rate = 0.46 mg/kg/day (range: 0.33-0.60 mg/kg/day). Flumethrin: Mean dosage rate = 0.088 mg/kg/day (range: 0.06-0.12 mg/kg/day).

The dosage rates from a ~35 g dog collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (23-91 day) Dog & Puppy Studies: Imidacloprid: Mean dosage rate = 1.49 mg/kg/day (range: 0.70-2.44 mg/kg/day). Flumethrin: Mean dosage rate = 0.24 mg/kg/day (range: 0.07-0.42 mg/kg/day).

Long-term (238-245 day) Dog Studies: Imidacloprid: Mean dosage rate = 0.42 mg/kg/day (range: 0.33-0.52 mg/kg/day). Flumethrin: Mean dosage rate = 0.12 mg/kg/day (range: 0.09-0.18 mg/kg/day).

ED_005739A_00099540-00003

This report is classified as acceptable (Non-Guideline). It provides useful information regarding the rates of release of the two active ingredients from a collar containing ~10% Imidacloprid and ~4.5% Flumethrin and the exposure to cats and dogs wearing this collar.

COMPLIANCE: Signed and dated GLP (noting that this study was not conducted in full compliance with GLP standards), and Data Confidentiality statements were provided. There is no Quality Assurance Statement (presumably because this report represents a review compilation).

RESULTS:

Collars were weighed, then worn by cats or dogs for varying periods of time, after which they were weighed and analyzed for content of the two active ingredients.

Cat studies:

Dosage rates in cat studies (from Table 5 on p. 8 of MRID 48240140):

Study Number	Breed & (body weight range in kg)	Study Duration (Days)	Imidacloprid exposure (mg/kg/day)	Flumethrin exposure (mg/kg/day)
146.266	DSH (3.3-5.1)	2	7.36	0.18
		7	4.73	0.18
		14	3.03	0.23
		28	2.08	0.12
		56	1.44	0.10
		84	1.13	0.18
146.164	DSH (2.3-5.1)	30	3.04	0.44
		238	0.56	0.12
146.303	DSH (3.7-4.7)	238	0.39	0.06
146.159	Mix (2.1-4.7)	60	1.27	0.20
152.152	DSH (2.8-5.3)	61	1.62	0.32
152.150	DSH kittens (0.97-1.26 study day 0)	30	3.72	0.20
		60	1.91	0.14
146.747	DSH (3.6-5.7)	28	0.71	0.05
146.156	DSH (2.8-5.3)	238	0.42	0.07
146.045	DSH (3.8-7.0)	241	0.33	0.10
146.155	DSH (2.7-	240	0.60	0.09

There are two mechanisms by which an active can be released from a collar: 1) Simple wear, and 2) Diffusion from the matrix. An approximation of the amount of an active released from wear can be calculated by: weight loss – (amount of imidacloprid lost + amount of flumethrin loss) = amount of plastic lost. Then: (amount of plastic lost)/[1 – (original percentage of imadocloprid + original percentage of flumethrin)] = total amount lost by wear. Then: (total amount lost by wear) x (original percentage of imadocloprid) = amount of imidacloprid lost by wear , and: (total amount lost by wear) x (original percentage of flumethrin) = amount of flumethrin lost by wear. The table below shows that for the cat collar most of the imidacloprid is released by diffusion (the total amount released by wear is approximately 10-14% for 28 days and about 42% for 240 days), while most of the flumethrin is released by wear (the mean total percentage released by wear in the 5 cat studies below which ran for 238-241 days is 99.46%).

Study Number	Body weight range in kg	Study Duration (Days)	Mean collar weight loss (mg)	Plastic weight loss (mg)	Amount of Imidaclo prid released (mg)	Amount of flumethrin released (mg)	Amount in mg of imidacloprid released by wear and % total	Amount in mg of flumethrin released by wear (% total released)
146.156	3.2-5.4	238	2024.44	1518.97	433.1	72.37	179.64 (41.48)	80.04 (110.6)
146.164	2.56-4.22	30	1198.75	860.75	295.58	42.43	100.67 (34.06)	45.30 (106.8)
	2.28-5.14	240	2160.0	1634.56	435.3	90.14	191.18 (43.92)	86.03 (95.44)
146.159	2.4-4.7	60	907.33	634.99	235.60	36.74	72.61 (30.82)	33.34 (90.75)
146.303	3.7-4.7	238	1798.75	1340.35	394.45	63.95	158.52 (40.19)	70.63 (110.44)
146.747	3.6-5.7	28	458.75	239.71	205.34	13.7	27.38 (13.33)	12.29 (89.73)
146.266	3.5-4.1	2	33.33	N.V.	54.67	1.53	N.C.	N.C.
	3.4-5.1	7	133.33	16.36	109.0	7.97	1.93 (1.77)	0.86 (10.82)
	3.4-5.1	14	266.67	103.57	149.5	13.60	12.25 (8.19)	5.46 (40.13)
	3.4-5.1	28	366.67	160.01	195.53	11.13	18.92 (9.68)	8.43 (75.75)
	3.5-5.1	56	633.33	344.69	266.87	21.77	40.77 (15.28)	18.16 (83.43)
	3.3-3.7	84	1000.00	648.2	312.4	39.40	76.66 (24.54)	34.16 (86.69)
146.045	4.6-6.0	241	2197.0	1656.37	411.21	129.42	195.89 (47.64)	87.28 (67.44)
146.155	2.5-3.6	240	1804.0	1334.52	407.48	62.00	157.83 (38.73)	70.32 (113.42)
146.100	2.38-5.8	226[a]	1502.5[a]	1294.77[a]	177.54[a]	30.19[a]	33.98 (19.14)	30.59 (101.31)
	2.58-3.36	226[b]	1696.25[b]	1315.76[b]	349.89[b]	30.60[b]	70.93 (20.27)	31.92 (104.31
	2.28-4.36	226[c]	1725.0[c]	1402.13[c]	297.44[c]	25.43[c]	159.79 (53.72)	35.95 (141.37)

Data calculated from information (Tables) on p. 36, 37, 38, 39, 40, 41, 42

[a]Collar supposedly contained 2.5% Imidacloprid and 2.25% Flumethrin and this reviewer's calculations above are based on that composition; however, column 6 of the Table on p. 44 of MRID 48240140 indicates the collar contained 10.1% Imidacloprid and column 7 indicates it contained 4.5% Flumethrin.

[b]Collar supposedly contained 5.0% Imidacloprid and 2.25% Flumethrin and this reviewer's calculations above are based on that composition; however, column 6 of the Table on p. 44 of MRID 48240140 indicates the collar contained 10.1% Imidacloprid and column 7 indicates it contained 4.5% Flumethrin.

[c]Collar supposedly contained 10.0% Imidacloprid and 2.25% Flumethrin and this reviewer's calculations above are based on that composition; however, column 6 of the Table on p. 44 of MRID 48240140 indicates the collar contained 10.1% imidacloprid and column 7 indicates it contained 4.5% Flumethrin.

Dog studies:

Dosage rates in dog studies (from Table 6 on p. 8 of MRID 48240140):

Study Number	Breed & (body weight range in kg)	Study Duration (Days)	Imidacloprid exposure (mg/kg/day)	Flumethrin exposure (mg/kg/day)
146.165	Mongrel (11.6-19.4)	30	1.62	0.20
		238	0.33	0.11
146.306	Beagle (9.4-13.6)	238	0.52	0.18
146.161	Mix (8.4-20.2)	60	0.89	0.07
152.151	Beagle (8.7-13.4)	60	1.37	0.15
152.149	Beagle puppies (1.5-2.9 on study day 0)	23	2.44	0.36
		30	2.21	0.42
		60	0.97	0.28
146.737	Beagle (8.7-11.7)	28	2.25	0.20
146.158	Beagle (8.8-12.8)	245	0.52	0.11
146.390	Beagle (6.6-20.4)	240	0.35	0.09
146.592	Beagle (8.3-13.5)	240	0.37	0.13
146.269	Mongrel (7.1-21.5)	90	0.70	0.32
146.607	Beagle (10.0-13.1)	91	0.97	0.18

The table below shows that for the dog collar most of the imidacloprid is released by diffusion (the total amount released by wear is approximately 8-22% for 28-30 days and about 29-61.5%, with a mean of ~44% for 238-245 days), while most of the flumethrin is released by wear (the mean total percentage released by wear in the 5 dog collar studies below which ran for 238-245 days was 64.4%).

Study Number	Body weight range in kg)	Study Duration (Days)	Mean collar weight loss (mg)	Plastic weight loss (mg)	Amount of Imidacloprid released (mg)	Amount of flumethrin released (mg)	Amount in mg of imidacloprid released from wear and % total	Amount in mg of flumethrin released from wear (% total released)
146.164	(11.6-19.4)	30	2145.7	1342.5	715.74	87.49	155.26 (21.69)	70.57 (80.66)
		240	6921.4	5155.95	1310.19	455.26	596.31 (45.51)	271.05 (59.54)
146.158	(8.8-12.8)	245	5136.0	3481.85	1358.7	295.45	406.76 (29.94)	178.97 (60.58)
146.306	(9.4-13.6)	238	6238.8	4458.65	1321.25	458.9	520.87 (39.42)	229.18 (49.94)
146.362/ 146.607	(10.0-13.1)	91	3498.3	2319.43	998.3	180.57	268.25 (26.87)	104.37 (57.8)
146.737	(9.1-11.0)	28	1142.5	445.99	640.61	55.9	51.58 (8.05)	23.45 (41.95)
146.390	(10.4-18.2)	240	5718.0	4297.67	1126.98	303.35	500.90 (44.45)	220.39 (72.65)
146.269	(7.22-21.48)	90	3696.25#	2621.89	796.3	278.06	303.23 (38.08)	137.83 (49.57)
146.161	(10.36-17.56)	60	1633.75	797.53	797.61	38.61	92.24 (11.56)	41.93 (108.59)
146.592	(8.3-13.5)	240	6467.14	5156.91	969.07	341.16	596.42 (61.5)	271.10 (79.46)

Data calculated from information (Tables) on p. 45, 46, 47, 48, 49, 50, 51, 52, and 53.
#No weight loss reported for collar from one dog (CC0CE2); data from this dog not included in calculations by the EPA reviewer.

For the dog studies that ranged from 238-245 days the mean collar weight loss was 6096.27 (range: 5136.0-6921.4) mg; the mean plastic (matrix) weight loss was 4510.21 (range: 3481.85-5156.91) mg; the mean total amount of imidacloprid released per collar was 1217.24 (range: 969.07-1358.7) mg; and the mean total amount of flumethrin released per collar was 370.82 (range: 295.45-458.9) mg. The approximate amount of imidacloprid released per collar from wear was 524.25 (range: 406.76-596.42) mg and the approximate amount of flumethrin released per collar from wear was 234.14 (range: 178.97-271.1) mg.

The following summarizes the dosages given in Tables 5 and 6 on p. 8 of MRID 48240140:

Short-Term (28-91 day) Cat & Kitten Studies:	Imidacloprid exposure (mg/kg/day): 2.08, 1.44, 1.13, 3.04, 1.27, 1.62, 3.72*, 1.91*, 0.71 **[Mean = 1.88]**	Flumethrin exposure (mg/kg/day): 0.12, 0.10, 0.18, 0.44, 0.20, 0.32, 0.20*, 0.14*, 0.05 **[Mean = 0.19]**
Long-Term (238-245 day) Cat Studies:	Imidacloprid exposure (mg/kg/day): 0.56, 0.39, 0.42, 0.33, 0.60 **[Mean = 0.46]**	Flumethrin exposure (mg/kg/day): 0.12, 0.06, 0.07, 0.10, 0.09 **[Mean = 0.088]**
Short-Term (23-91 day) Dog & Puppy Studies:	Imidacloprid exposure (mg/kg/day): 1.62, 0.89, 1.37, 2.44**, 2.21**, 0.97**, 2.25, 0.70, 0.97 **[Mean = 1.49]**	Flumethrin exposure (mg/kg/day): 0.20, 0.07, 0.15, 0.36**, 0.42**, 0.28**, 0.20, 0.32, 0.18 **[Mean = 0.24]**
Long-Term (238-245 day) Dog Studies:	Imidacloprid exposure (mg/kg/dau): 0.33, 0.52, 0.52, 0.35, 0.37 **[Mean = 0.42]**	Flumethrin exposure (mg/kg/day): 0.11, 0.18, 0.11, 0.09, 0.13 **[Mean = 0.12]**

*Kitten study
**Puppy study

Reviewer's Conclusions:

The dosage rates from a ~10 g cat collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (28-91 day) Cat & Kitten Studies: Imidacloprid: Mean dosage rate = 1.88 mg/kg/day (range: 0.71-3.72 mg/kg/day). Flumethrin: Mean dosage rate = 0.19 mg/kg/day (range: 0.05-0.44 mg/kg/day).

Long-term (238-245 day) Cat Studies: Imidacloprid: Mean dosage rate = 0.46 mg/kg/day (range: 0.33-0.60 mg/kg/day). Flumethrin: Mean dosage rate = 0.088 mg/kg/day (range: 0.06-0.12 mg/kg/day).

The dosage rates from a ~35 g dog collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (23-91 day) Dog & Puppy Studies: Imidacloprid: Mean dosage rate = 1.49 mg/kg/day (range: 0.70-2.44 mg/kg/day). Flumethrin: Mean dosage rate = 0.24 mg/kg/day (range: 0.07-0.42 mg/kg/day).

Long-term (238-245 day) Dog Studies: Imidacloprid: Mean dosage rate = 0.42 mg/kg/day (range: 0.33-0.52 mg/kg/day). Flumethrin: Mean dosage rate = 0.12 mg/kg/day (range: 0.09-0.18 mg/kg/day).

This report is classified as acceptable (Non-Guideline). It provides useful information regarding the rates of release of the two active ingredients from a collar containing ~10% Imidacloprid and ~4.5% Flumethrin and the exposure to cats and dogs wearing this collar.

ACUTE TOX ONE-LINERS:

1. DP BARCODE: 392118				
2. PC CODES: 129099 (Imidacloprid); 036007 (Flumethrin)				
3. CURRENT DATE: December 29, 2011				
4. TEST MATERIAL: Dog & Cat Collars containing ~10% Imidacloprid & ~4.5% Flumethrin				
Study/Species/Lab Study # / Date	**MRID**	**Results**	**Tox. Cat.**	**Core Grade**
Dosages & release rates of actives (review compilation)/cats & dogs/ Bayer Animal Health, Monheim, Germany/PNR 1427/June 28, 2010	48240140	**Short-term (28-91 day) Cat & Kitten Studies:** Imidacloprid: Mean dosage rate = 1.88 mg/kg/day (range: 0.71-3.72 mg/kg/day). Flumethrin: Mean dosage rate = 0.19 mg/kg/day (range: 0.05-0.44 mg/kg/day). **Long-term (238-245 day) Cat Studies:** Imidacloprid: Mean dosage rate = 0.46 mg/kg/day (range: 0.33-0.60 mg/kg/day). Flumethrin: Mean dosage rate = 0.088 mg/kg/day (range: 0.06-0.12 mg/kg/day). The dosage rates from a ~35 g dog collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following: **Short-term (23-91 day) Dog & Puppy Studies:** Imidacloprid: Mean dosage rate = 1.49 mg/kg/day (range: 0.70-2.44 mg/kg/day). Flumethrin: Mean dosage rate = 0.24 mg/kg/day (range: 0.07-0.42 mg/kg/day). **Long-term (238-245 day) Dog Studies:** Imidacloprid: Mean dosage rate = 0.42 mg/kg/day (range: 0.33-0.52 mg/kg/day). Flumethrin: Mean dosage rate = 0.12 mg/kg/day (range: 0.09-0.18 mg/kg/day).	n/a	A (non-Guideline)

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived

Message

From: Goodis, Michael [Goodis.Michael@epa.gov]
Sent: 8/2/2016 1:18:26 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: RE: Pet Collars

OK...

Michael L. Goodis, P.E.
Acting Deputy Director, Registration Division (RD)
Office of Pesticide Programs (OPP)

Phone 703-308-8157
Room S7624

From: Echeverria, Marietta
Sent: Tuesday, August 02, 2016 9:12 AM
To: Goodis, Michael <Goodis.Michael@epa.gov>; Laws, Meredith <Laws.Meredith@epa.gov>
Cc: Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Lewis, Susan <Lewis.Susan@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>
Subject: RE: Pet Collars

Mike, we have a team meeting tomorrow. I can make a better recommendation about when to meet with PMRA **Ex. 5 Deliberative Process (DP)** after that meeting. Thanks

---

From: Goodis, Michael
Sent: Monday, August 01, 2016 9:01 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Laws, Meredith <Laws.Meredith@epa.gov>
Cc: Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Lewis, Susan <Lewis.Susan@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>
Subject: RE: Pet Collars

Seems like **Ex. 5 Deliberative Process (DP)**?
Maybe propose a meeting with PMRA later in August. I just need to get back with them on timing for now so let me know when would be a good day.

A separate briefing would be helpful. Feel free to set one up when ready...thanks

Michael L. Goodis, P.E.
Acting Deputy Director, Registration Division (RD)
Office of Pesticide Programs (OPP)

Phone 703-308-8157
Room S7624

From: Echeverria, Marietta
Sent: Monday, August 01, 2016 8:55 AM
To: Laws, Meredith <Laws.Meredith@epa.gov>; Goodis, Michael <Goodis.Michael@epa.gov>
Cc: Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Lewis, Susan <Lewis.Susan@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>
Subject: RE: Pet Collars

This is the Seresto collar (flumethrin/imidacloprid). We had a call with PMRA on 7/12. This product is registered here but pending registration at PMRA. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP) Flumethrin risk assessments for reg review are going out in September. Let me know if you'd like a briefing or if I can bring you up to speed during a general.

Thanks,
Marietta

From: Laws, Meredith
Sent: Friday, July 29, 2016 9:13 AM
To: Goodis, Michael <Goodis.Michael@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Lewis, Susan <Lewis.Susan@epa.gov>
Subject: RE: Pet Collars

Mike - I'm not sure exactly what the topic is about except t Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Meredith

From: Goodis, Michael
Sent: Friday, July 29, 2016 9:05 AM
To: Laws, Meredith <Laws.Meredith@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Rosenblatt, Daniel <Rosenblatt.Dan@epa.gov>; Lewis, Susan <Lewis.Susan@epa.gov>
Subject: Pet Collars

Meredith and Marietta

Please see the note below from PMRA about setting up a time to discuss flumethrin/imidicloprid pet collars.
I believe Ex. 5 Deliberative Process (DP) Can you fill me in on the topic to discuss and let me know whether we are ready to discuss with PMRA by mid-August?
I need to get back to them to set it up. Thanks

Michael L. Goodis, P.E.
Acting Deputy Director, Registration Division (RD)
Office of Pesticide Programs (OPP)

Phone 703-308-8157
Room S7624

From: Brander, Peter (HC/SC) [mailto:peter.brander@canada.ca]
Sent: Tuesday, July 26, 2016 4:42 PM
To: Goodis, Michael <Goodis.Michael@epa.gov>
Cc: Hart, Connie (HC/SC) <connie.hart@canada.ca>; Silva, Minoli (HC/SC) <minoli.silva@canada.ca>; O'Reilly, Joanna (HC/SC) <joanna.oreilly@canada.ca>; Sterkenburg, Neilda (HC/SC) <neilda.sterkenburg@canada.ca>; Lamarche, Natalie (HC/SC) <natalie.lamarche@canada.ca>
Subject: RE: Draft of the pyriofenone chronic bee study

Ex. 6 Personal Privacy (PP)

In my absence, should you agree that it would be of value to have our evaluators discuss the science further, I would ask that you contact Connie Hart, who I have copied on this email. Connie is aware of the file and would be able to assist in pulling together the HC particpants for such a discussion.

I was also wondering if we could look to book a meeting for mid-August as a follow-up to the recent discussion between PMRA and the EPA with regard to the review of flumethrin/imidicloprid pet collars. The PMRA had committed to a follow-up meeting with the EPA once we had met with Bayer on this file. I will look to have my EA book this meeting for mid August.

Thank you.

Peter J Brander

Chief Registrar and Director General, Pest Management Regulatory Agency
Health Canada / Government of Canada
peter.brander@canada.ca / Tel: 613-736-3704

Chef de l'homologation et Directeur général, Agence de réglementation de la lutte antiparasitaire
Sante Canada / Gouvernement du Canada
peter.brander@canada.ca / Tél : 613-736-3704

From: Goodis, Michael [mailto:Goodis.Michael@epa.gov]
Sent: 2016-07-25 12:11 PM
To: Brander, Peter (HC/SC)
Subject: RE: Draft of the pyriofenone chronic bee study

Hi Peter

Just letting you know that I got your voicemail and we are looking into it.
I will be in touch when we find out....

Michael L. Goodis, P.E.
Acting Deputy Director, Registration Division (RD)
Office of Pesticide Programs (OPP)

Phone 703-308-8157
Room S7624

From: Goodis, Michael
Sent: Tuesday, July 19, 2016 5:29 PM
To: 'Brander, Peter (HC/SC)' <peter.brander@canada.ca>
Cc: Lewis, Susan <Lewis.Susan@epa.gov>
Subject: FW: Draft of the pyriofenone chronic bee study

Hi Peter

Attached is the study review that we discussed. Let me know when you are ready to discuss again.

Michael L. Goodis, P.E.
Acting Deputy Director, Registration Division (RD)
Office of Pesticide Programs (OPP)

Phone 703-308-8157
Room S7624

From: McCall, Deborah
Sent: Tuesday, July 19, 2016 4:23 PM
To: Goodis, Michael <Goodis.Michael@epa.gov>
Subject: Draft of the pyriofenone chronic bee study

Attached is the draft copy of the pyriofenone chronic bee study.

Deborah McCall (Debbie)
Chief, Invertebrate & Vertebrate Branch 2
USEPA
Office of Pesticide Programs
1200 Pennsylvania Ave., NW (7505P)
Washington, DC 20460
703.605.0717
mccall.deborah @epa.gov

From: VA-PYS-7971-M@epa.gov [mailto:VA-PYS-7971-M@epa.gov]
Sent: Tuesday, July 19, 2016 4:25 PM
To: McCall, Deborah <McCall.Deborah@epa.gov>
Subject:

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 8/29/2016 4:53:22 PM
To: Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]
Subject: FW: Two Noteworthy Cases from NPIC (one involving seresto collar)
Attachments: 2016-7460.pdf; 2016-7313.pdf

Hi David –

Here is another reported incident regarding Seresto.

Thanks much,
Bo

From: Rivera-Lupianez, Ana
Sent: Monday, August 29, 2016 12:50 PM
To: Chen, Jonathan <Chen.Jonathan@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Miller, Robert <Miller.Robert@epa.gov>; Panger, Melissa <Panger.Melissa@epa.gov>; Rivera-Lupianez, Ana <Rivera-Lupianez.Ana@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>; Sell, Nathan <Sell.Nathan@epa.gov>; Tanner, Lee <Tanner.Lee@epa.gov>
Cc: Dumas, Richard <Dumas.Richard@epa.gov>; Miller, Robert <Miller.Robert@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Hopkins, Yvette <Hopkins.Yvette@epa.gov>; Steeger, Thomas <Steeger.Thomas@epa.gov>
Subject: Fw: Two Noteworthy Cases from NPIC (one involving seresto collar)

FYI
Two incidents reported to NPIC, one involving a seresto collar

Thanks,
Ana

Ana Rivera-Lupiáñez
Office of Pesticide Programs
Environmental Protection Agency
rivera-lupianez.ana@epa.gov
(703) 308-6841

From: Hallman, Amy S <Amy.Hallman@oregonstate.edu>
Sent: Monday, August 29, 2016 12:23 PM
To: Rivera-Lupianez, Ana
Cc: Buhl, Kaci J; Craig.Marcus@oregonstate.edu
Subject: Noteworthy Cases from NPIC

Hello Ana,

We had a noteworthy case reported recently that met the criteria for EPA referral. I'm also including an FYI regarding a Seresto flea collar incident.

Case 7460 (Group Animal/Wildlife Death): A caller reported the death of all butterflies on her property (about 50, in various life stages) after a public mosquito spraying for West Nile Virus. She did not have product information at the time of the call.

Case 7313 (Reaction to Seresto flea collar): A caller reported her dog had sores on its neck about 2 weeks after the collar was applied and the animal required veterinary treatment. She also expressed frustration at the response from the manufacturer.

Best,
Amy Hallman

--
Amy S. Hallman, MS
Interim Project Coordinator
National Pesticide Information Center
Oregon State University
Department of Environmental and Molecular Toxicology
amy.hallman@oregonstate.edu
541-737-6093

npic
NATIONAL PESTICIDE INFORMATION CENTER

2016 REFERRAL TO EPA **LOG: 7313**

Date: **August 1, 2016**

City, State: **Johnson City, NY**

Narrative: Caller wishing to report a reaction her dog (100 lb, 8 year old, intact male German shepherd) had to a dog collar, EPA registration number 11556-155 (active ingredients imidacloprid, flumethrin). Caller reported that she applied the collar to the dog on 06/29/2016, that he lives in an outdoor kennel, and that she noticed the next morning that the dog was shaking his head more than normal, but her husband had an accident that kept her from paying much attention to the dog for quite awhile. Caller reported that on 07/12/2016 she was visiting the dog in his outside kennel, touched his head and ears and noticed that they were very hot and felt like they were "on fire". Caller reported that she called her veterinarian, and was told to check the dog's neck to see if he had sores, and if he did to remove the collar and bathe him. Caller reported that the dog did have noticeable oozing sores on his neck, she washed him with Dawn dish soap, and the veterinarian prescribed antibiotics and steroids to help with the inflammation without a clinic visit.

Caller reported that she took the dog into the veterinarian on 07/19/2016 because his symptoms seemed to continue, and the vet shaved the dog around his neck and down to his shoulder blades because the sores covered that entire area. Caller reported that the dog had an ear infection also, and was prescribed another antibiotic, and another cream ointment. Caller reported that she has been using a medicated shampoo on the dog, and has had to move him indoors while he has open wounds on his skin. Caller reported that she that she has been incredibly disappointed with the response of the manufacturer (Bayer Healthcare) to her situation. Caller reported she is planning on doing everything she can to try to stop other consumers from going through a similar experience.

Discussed NPIC services. Discussed the registration of products through both federal and state agencies, and provided contact information for the State Lead Pesticide Agency as a resource for reporting concerning pesticides. Resources used: Registration Decision for Flumethrin for Use in Cat and Dog Collars - 2012, NPIC Fact Sheet, & Hazardous Substances Data Bank (HSDB).

Message

From: Bacon, Laura [Bacon.Laura@epa.gov]
Sent: 8/22/2016 6:05:48 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: RE: Seresto - Human Exposure Analysis document

Thanks. I had forwarded it to a few of the HED folks, but I will forward to others as well.

Laura Bacon (Nollen)
Acting Product Manager 4
Invertebrate-Vertebrate Branch 1
Registration Division, Cube S-7213
Office of Pesticide Programs

U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Phone: (703) 305-7390

From: Echeverria, Marietta
Sent: Monday, August 22, 2016 1:55 PM
To: Bacon, Laura <Bacon.Laura@epa.gov>
Subject: RE: Seresto - Human Exposure Analysis document

PRD: Melanie Biscoe, Maria Piansay, Linda Arrington
HED: Donna Davis, David Miller, Shanna Recore, Elizabeth Evans
EFED: Colleen Rossmeisel
RD: Julie Breeden, me

From: Bacon, Laura
Sent: Friday, August 19, 2016 4:40 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>
Subject: FW: Seresto - Human Exposure Analysis document

Hi Marietta,

For Seresto human case critique can you let me know whom to forward this to? Bo and I met to talk about issues for next week, but we did not specifically talk about this action.

Thanks,

Laura Bacon (Nollen)
Acting Product Manager 4
Invertebrate-Vertebrate Branch 1
Registration Division, Cube S-7213
Office of Pesticide Programs

U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Phone: (703) 305-7390

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Friday, August 19, 2016 4:24 PM
To: Bacon, Laura <Bacon.Laura@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Bruce Martin <bruce.martin@bayer.com>; laura.becon@epa.gov
Subject: FW: Seresto - Human Exposure Analysis document

Dear Ms. Bacon,
After sending the following email, I received a message back that Mr. Davis will be out next week and that you are the contact for these types of actions while he is on vacation. Please confirm that you received this email and the Confidential attachment, and have forwarded it as requested. If this is "out of context" for you, you may want to discuss the background of this situation with Ms. Echeverria.

Thank you, and do not hesitate to call if you have questions.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

From: Doug Spilker
Sent: Friday, August 19, 2016 3:10 PM
To: 'Davis, Kable'
Cc: Echeverria, Marietta; Miller.davidj@Epa.gov; 'Rossmeisl.colleen@Epa.gov'; 'Adler, Bonnie'; Bruce Martin
Subject: Seresto - Human Exposure Analysis document

Dear Mr. Davis,
Bayer became aware at the meeting with the Agency on 17 Aug 2016 that EPA is in the final stage of conducting a safety review of pyrethroids, including Flumethrin (one of the active ingredients in Seresto pet collar), and were invited to submit any relevant information until end of this week.

Ex. 4 CBI - Potential Claims

Ex. 4 CBI - Potential Claims

Please forward this CONFIDENTIAL information to the appropriate Agency staff as soon as possible, for their immediate use and consideration.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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Message

From: Fry, Meridith [Fry.Meridith@epa.gov]
Sent: 6/23/2016 11:54:00 AM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]
CC: Saunders, Jennifer [Saunders.Jennifer@epa.gov]
Subject: RE: Notes from Pyrethroid Team Meeting 6/22

Ex. 5 Deliberative Process (DP)

Meridith

Meridith Fry, Ph.D.
Acting Product Manager 4
Invertebrate & Vertebrate Branch 1, S7213
Registration Division (7505P)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Email: Fry.Meridith@epa.gov
Phone: 703.347.0128
Fax: 703.305.0204

From: Echeverria, Marietta
Sent: Thursday, June 23, 2016 7:51 AM
To: Fry, Meridith <Fry.Meridith@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>
Cc: Saunders, Jennifer <Saunders.Jennifer@epa.gov>
Subject: RE: Notes from Pyrethroid Team Meeting 6/22

I'm unclear on Donna Davis' comments 1 (a)

From: Fry, Meridith
Sent: Wednesday, June 22, 2016 4:18 PM
To: Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Saunders, Jennifer <Saunders.Jennifer@epa.gov>
Subject: Notes from Pyrethroid Team Meeting 6/22

Hi all,

I went to the Pyrethroid Team Meeting today. Here is a quick update on the two RD items we discussed.

1) Enhanced Reporting Pilot for Pet Spot-Ons – I shared that we have 2 participants/volunteers currently, and 1 additional interested. Also I let the team know that we do not have an update from PMRA yet on Seresto (flumethrin).
   a. **Ex. 5 Deliberative Process (DP)**

b. Ex. 5 Deliberative Process (DP)

2) Ex. 5 Deliberative Process (DP)

Thanks,
Meridith

Meridith Fry, Ph.D.
Acting Product Manager 4
Invertebrate & Vertebrate Branch 1, S7213
Registration Division (7505P)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Email: Fry.Meridith@epa.gov
Phone: 703.347.0128
Fax: 703.305.0204

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 6/23/2016 11:40:46 AM
To: Fry, Meridith [Fry.Meridith@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]
CC: Saunders, Jennifer [Saunders.Jennifer@epa.gov]
Subject: RE: Notes from Pyrethroid Team Meeting 6/22

Excellent. Thanks, Meridith!

From: Fry, Meridith
Sent: Wednesday, June 22, 2016 4:18 PM
To: Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Saunders, Jennifer <Saunders.Jennifer@epa.gov>
Subject: Notes from Pyrethroid Team Meeting 6/22

Hi all,

I went to the Pyrethroid Team Meeting today. Here is a quick update on the two RD items we discussed.

1) Enhanced Reporting Pilot for Pet Spot-Ons – I shared that we have 2 participants/volunteers currently, and 1 additional interested. Also I let the team know that we do not have an update from PMRA yet on Seresto (flumethrin).
   a.
   b. Ex. 5 Deliberative Process (DP)

2) Ex. 5 Deliberative Process (DP)

Thanks,
Meridith

Meridith Fry, Ph.D.
Acting Product Manager 4
Invertebrate & Vertebrate Branch 1, S7213

Registration Division (7505P)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Email: Fry.Meridith@epa.gov
Phone: 703.347.0128
Fax: 703.305.0204

Message

From: Doug Spilker [doug.spilker@bayer.com]
Sent: 8/22/2016 3:42:45 PM
To: Bacon, Laura [Bacon.Laura@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Bruce Martin [bruce.martin@bayer.com]; laura.becon@epa.gov; Davis, Kable [Davis.Kable@epa.gov]
Subject: RE: Seresto - Statisical Analysis methods
Attachments: Bayer AH Seresto Internal Analysis Slides - Stats 20160822.pdf

Dear Laura,

Thank you for handling the information while Bo Davis is out. We appreciate your responsiveness. In addition to the document we sent to you on Friday, there was still one action item for us that came out of the meeting we had with the Agency on August 17th. Dr. David Miller (HED) and Dr. Colleen Rossmeisl requested that we send the statistical analysis methods that we used in our internal analyses that supported our conclusions on slide 9 (titled: "Recap: Bayer's Findings regarding Seresto AE profile.")

To that end, please find attached the respective information. Please forward to Drs. Miller and Rossmeisl as soon as possible.

Thank you again for handling these actions, and if you have any questions, please call me (913-268-2751) or Dr. Bruce Martin (913-268-2779.)

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

From: Bacon, Laura [mailto:Bacon.Laura@epa.gov]
Sent: Friday, August 19, 2016 3:45 PM
To: Doug Spilker
Cc: Echeverria, Marietta; Bruce Martin; laura.becon@epa.gov
Subject: RE: Seresto - Human Exposure Analysis document

Good afternoon Doug,

This message is to confirm that I have received the attached document. As per my voicemail, I will let you know when I have forwarded this along since I am uncertain of the contact. I will let you know on Monday when I have forwarded it along, and I will let them know that I received it this Friday.

FYI- Bo brought to my attention that my e-mail address is incorrectly listed in the EPA lookup database, but you are correct that bacon.laura@epa.gov is the correct address.

Thank you,

Laura Bacon (Nollen)
Acting Product Manager 4
Invertebrate-Vertebrate Branch 1
Registration Division, Cube S-7213
Office of Pesticide Programs

U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Phone: (703) 305-7390

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Friday, August 19, 2016 4:24 PM
To: Bacon, Laura <Bacon.Laura@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Bruce Martin <bruce.martin@bayer.com>; laura.becon@epa.gov
Subject: FW: Seresto - Human Exposure Analysis document

Dear Ms. Bacon,
After sending the following email, I received a message back that Mr. Davis will be out next week and that you are the contact for these types of actions while he is on vacation. Please confirm that you received this email and the Confidential attachment, and have forwarded it as requested. If this is "out of context" for you, you may want to discuss the background of this situation with Ms. Echeverria.

Thank you, and do not hesitate to call if you have questions.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

From: Doug Spilker
Sent: Friday, August 19, 2016 3:10 PM
To: 'Davis, Kable'
Cc: Echeverria, Marietta; Miller.davidj@Epa.gov; 'Rossmeisl.colleen@Epa.gov'; 'Adler, Bonnie'; Bruce Martin
Subject: Seresto - Human Exposure Analysis document

Dear Mr. Davis,

Bayer became aware at the meeting with the Agency on 17 Aug 2016 that EPA is in the final stage of conducting a safety review of pyrethroids, including Flumethrin (one of the active ingredients in Seresto pet collar), and were invited to submit any relevant information until end of this week.

Ex. 4 CBI - Potential Claims

Please forward this CONFIDENTIAL information to the appropriate Agency staff as soon as possible, for their immediate use and consideration.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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Message

From: Doug Spilker [doug.spilker@bayer.com]
Sent: 8/19/2016 8:10:12 PM
To: Davis, Kable [Davis.Kable@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Adler, Bonnie [Adler.Bonnie@epa.gov]; Bruce Martin [bruce.martin@bayer.com]
Subject: Seresto - Human Exposure Analysis document
Attachments: Human Case Assessment Critique 2016_08_19.pdf

Dear Mr. Davis,

Bayer became aware at the meeting with the Agency on 17 Aug 2016 that EPA is in the final stage of conducting a safety review of pyrethroids, including Flumethrin (one of the active ingredients in Seresto pet collar), and were invited to submit any relevant information until end of this week.

Ex. 4 CBI - Potential Claims

Please forward this CONFIDENTIAL information to the appropriate Agency staff as soon as possible, for their immediate use and consideration.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 8/19/2016 1:45:56 PM
To: Doug Spilker [doug.spilker@bayer.com]
CC: Bruce Martin [bruce.martin@bayer.com]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: RE: Seresto/Flumethrin - Study Design Review

Understood. Thanks, Doug.

Kable Bo Davis
Product Manager 3
Invertebrate & Vertebrate Branch 1
(703) 306-0415
davis.kable@epa.gov

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Friday, August 19, 2016 9:38 AM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Bruce Martin <bruce.martin@bayer.com>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: RE: Seresto/Flumethrin - Study Design Review

Hi Bo,

Thank you for your response. We see the importance of these studies, so we plan to go ahead with our current study designs.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

From: Davis, Kable [mailto:Davis.Kable@epa.gov]
Sent: Friday, August 19, 2016 6:20 AM
To: Doug Spilker
Cc: Bruce Martin; Echeverria, Marietta
Subject: RE: Seresto/Flumethrin - Study Design Review

Hi Doug –

I hope all is well. The Agency is focusing now on completing our review of the Seresto incidents and should have a completed document within the upcoming weeks. Let's table the discussion on whether we need to review the study design until after we have forwarded you our review.

Have a nice weekend.
Bo

Kable Bo Davis
Product Manager 3
Invertebrate & Vertebrate Branch 1
(703) 306-0415
davis.kable@epa.gov

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Thursday, August 18, 2016 2:19 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Bruce Martin <bruce.martin@bayer.com>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: Seresto/Flumethrin - Study Design Review

Dear Mr. Davis,
One of the action items out of the meeting yesterday (8/17/2016) was for you to discuss with the appropriate expert in HED on whether they would want to review the study designs for the proposed toxicology/pharmacokinetic (PK) studies that we discussed, and are outlined in the presentation being sent to you under separate cover.

If the Agency wishes to review the study designs, we would also need guidance whether they would need to be submitted as a PRIA action(s).

We are eager to start these studies, so if we are asked to submit for review, we would request expedited reviews.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 8/18/2016 6:20:27 PM
To: Doug Spilker [doug.spilker@bayer.com]
CC: Bruce Martin [bruce.martin@bayer.com]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: RE: Seresto/Flumethrin - Study Design Review

Hi Doug –

I'll find out and will get back with you.

Thanks,
Bo

Kable Bo Davis
Product Manager 3
Invertebrate & Vertebrate Branch 1
(703) 306-0415
davis.kable@epa.gov

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Thursday, August 18, 2016 2:19 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Bruce Martin <bruce.martin@bayer.com>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: Seresto/Flumethrin - Study Design Review

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We are eager to start these studies, so if we are asked to submit for review, we would request expedited reviews.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
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Message

From: Doug Spilker [doug.spilker@bayer.com]
Sent: 8/18/2016 6:17:01 PM
To: Davis, Kable [Davis.Kable@epa.gov]
CC: Bruce Martin [bruce.martin@bayer.com]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: Seresto Meeting of August 17, 2016 - Copy of Presentation (CBI)
Attachments: Seresto Presentation to EPA Aug 17-2016 Share with EPA.pdf

Dear Mr. Davis,

As requested, please find attached a copy of our presentation from the Seresto Meeting with the Agency on August 17, 2016. This entire document contains Confidential Business Information, is marked as such, and should be handled appropriately as CBI within the Agency.

Please ensure that this document is provided as soon as possible to all EPA attendees to the meeting, and any other staff that would benefit from the information.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

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Message

From: Miller, David [Miller.DavidJ@epa.gov]
Sent: 6/9/2016 6:10:55 PM
To: Davis, Kable [Davis.Kable@epa.gov]
CC: Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Nguyen, James [Nguyen.James@epa.gov]; Sarkar, Bayazid [Sarkar.Bayazid@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Evans, Elizabeth [Evans.Elizabeth@epa.gov]
Subject: FW: Bayer Slides
Attachments: Seresto slides for Bayer meeting 6-9-16 (002)_BS_6_8_16 sr_DJM3.pptx

Yes, that's the final version.

Are you planning on passing out hard copies to Bayer or just projection it on screen. Note that the title slide and footer say not for distribution, citation, etc.

If we are going to share with Bayer, then this should come off.

My preference – if you want or feel a need to share with Bayer – tell them we will email them copies after the meeting.

Also- at some point – we should probably share with PMRA and communicate with PMRA about what ensued here today.

David

From: Davis, Kable
Sent: Thursday, June 09, 2016 1:48 PM
To: Miller, David <Miller.DavidJ@epa.gov>
Subject: FW: Bayer Slides

Is this the final version? It still says draft.

From: Miller, David
Sent: Thursday, June 09, 2016 10:45 AM
To: Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Nguyen, James <Nguyen.James@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: Bayer Slides

Yes, I noted that too – but considered Ex. 5 Deliberative Process (DP) So I

Ex. 5 Deliberative Process (DP)

Here is the most updated one.

From: Rossmeisl, Colleen
Sent: Thursday, June 09, 2016 9:51 AM
To: Davis, Kable <Davis.Kable@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Nguyen, James

<Nguyen.James@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: Bayer Slides

Ex. 5 Deliberative Process (DP)

Also, just wondering Ex. 5 Deliberative Process (DP) h? Just wondering Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)

From: Davis, Kable
Sent: Thursday, June 09, 2016 9:43 AM
To: Miller, David <Miller.DavidJ@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>
Cc: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Nguyen, James <Nguyen.James@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: Bayer Slides

David –

Do you think we should delete the last slide altogether? I have a feeling Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)

From: Miller, David
Sent: Thursday, June 09, 2016 9:10 AM
To: Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>
Cc: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Nguyen, James <Nguyen.James@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: Bayer Slides

Ok. Here are those edits.

From: Breeden-Alemi, Julie
Sent: Thursday, June 09, 2016 8:27 AM
To: Miller, David <Miller.DavidJ@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>
Cc: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Nguyen, James <Nguyen.James@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: Bayer Slides

Good morning!

Marietta, Bo, and I just met and reviewed the slides for the meeting today with Bayer. One point that came was that it seems that Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Many thanks, and please let us know if you have further discussion,
Julie

Julie A. Breeden-Alemi, DVM

U.S. Environmental Protection Agency
OCSPP / OPP / RD / IVB1
Breeden-Alemi.Julie@epa.gov
Phone: 703.347.0511
Office: S-7216, Mail Code: 7505P

From: Miller, David
Sent: Wednesday, June 08, 2016 4:05 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>
Cc: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Nguyen, James <Nguyen.James@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: Bayer Slides

Still finalizing these up, but here's the meat.

I'm here for a while if you want to talk. I will send around second draft later tonight for review tomorrow.

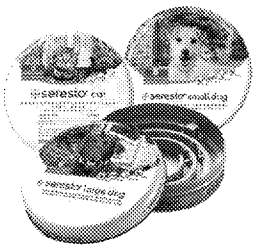
We probably want to add in a few slides regarding **Ex. 5 Deliberative Process (DP)** Shanna can add those in tomorrow am – she is at at 6 am.

David J. Miller CAPT | USPHS
Chief, Chemistry & Exposure Branch
and Acting Chief, Toxicology & Epidemiology Branch
Health Effects Division
Office of Pesticide Programs
703-305-5352 (voice)
703-305-5147 (fax)

Visit www.epa.gov/pesticides

WORKING DRAFT: NOT FOR CITATION, QUOTATION OR DISTRIBUTION

Review of Seresto Pet Collar Incidents Data



Presentation for Bayer
June 9th, 2016

U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (HED)

Seresto Overview

- Seresto: pet collar (dog & cat) containing 4.5% flumethrin and 10.0% imidacloprid
    - Intended to provide 8 months of control for fleas and ticks
- Submitted on September 23, 2010 as part of a new AI; Non-Food; Indoor Use submission for flumethrin
    - Seresto (EPA Reg. No. 11556-155) is currently the only registered end-use product for flumethrin
- Registered on March 16, 2012
- Currently Pending Registration with PMRA
    - Working closely with PMRA on analysis
    - Reviewed PMRA's Plausibility Analysis
    - Will review PMRA's Causality Analysis
- In Europe there are 4 Seresto collars authorized: one for cats, one for cats and dogs, one for small dogs (<8kg), and one for large dogs (>8kg).

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Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

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Ex. 5 Deliberative Process (DP)

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Ex. 5 Deliberative Process (DP)

combined the following:

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Ex. 5 Deliberative Process (DP)

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Ex. 5 Deliberative Process (DP)

Seresto last 8 months = 8,000 pet months of exposure whereas Spot-ons = 1,000 pet months of exposure

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Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

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END

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Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Timeline of Initial Bayer Communications

- 7/27/15: EPA received a press inquiry re: Seresto
  "Is EPA aware of any incidents surrounding Seresto and are there any ongoing investigations?"

- 7/29/15; first call with Bayer
  - Objective of call was to ask if they are aware of a high number of reported incidents

- 7/30/15; second call with Bayer
  - Objective of call was to request submission of incident data

- 7/30/15; Bayer emails sample of enhanced reporting format

- 8/3/15; Bayer emails incident information that was originally submitted to PMRA and published information regarding "Weber Effect"
  - Format Issues

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Ex. 5 Deliberative Process (DP)

DA – Death – if the domestic animal died or was euthanized;
DB – Major – if the domestic animal exhibited or was alleged to have exhibited symptoms which may have been life-threatening or resulted in residual disability;
DC – Moderate – if the domestic animal exhibited or was alleged to have exhibited symptoms which are more pronounced, more prolonged or of a more systemic nature than minor symptoms and included some treatment and return to pre-exposure state;
DD – Minor – if the domestic animal was alleged to have exhibited symptoms, but they were minimally bothersome and resolved rapidly;
DE – Unknown – if symptoms are unknown or not specified.

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Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

DRAFT - DO NOT CITE

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 8/15/2016 2:08:31 PM
To: Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]
Subject: FW: EU report on Seresto
Attachments: ANMV-Ra-Pharmacovigilance2012EN.pdf; EU SPC Seresto 2016.doc; EU Post Auth Assess Seresto 2016.doc

Hi David and Colleen --

PMRA forwarded us the EU's review of Seresto.

Thanks,
Bo

From: Godfrey, Victoria (HC/SC) [mailto:victoria.godfrey@canada.ca]
Sent: Monday, August 15, 2016 10:03 AM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Bruce, Dana (HC/SC) <dana.bruce@canada.ca>
Subject: EU report on Seresto

Hi Bo,

Dana indicated that you were looking for the EU's review of Seresto. Although I have never been able to find the full review, I am attaching the first pharmacovigilance report on Seresto in 2013 (from France), as well as the Summary of Product Characteristics and Post Authorization Assessment (from UK).

The links are also below if you need them.

Hope this helps

Vicky

https://www.anses.fr/en/system/files/ANMV-Ra-Pharmacovigilance2012EN.pdf

http://www.vmd.defra.gov.uk/ProductInformationDatabase/Default.aspx

Victoria Godfrey

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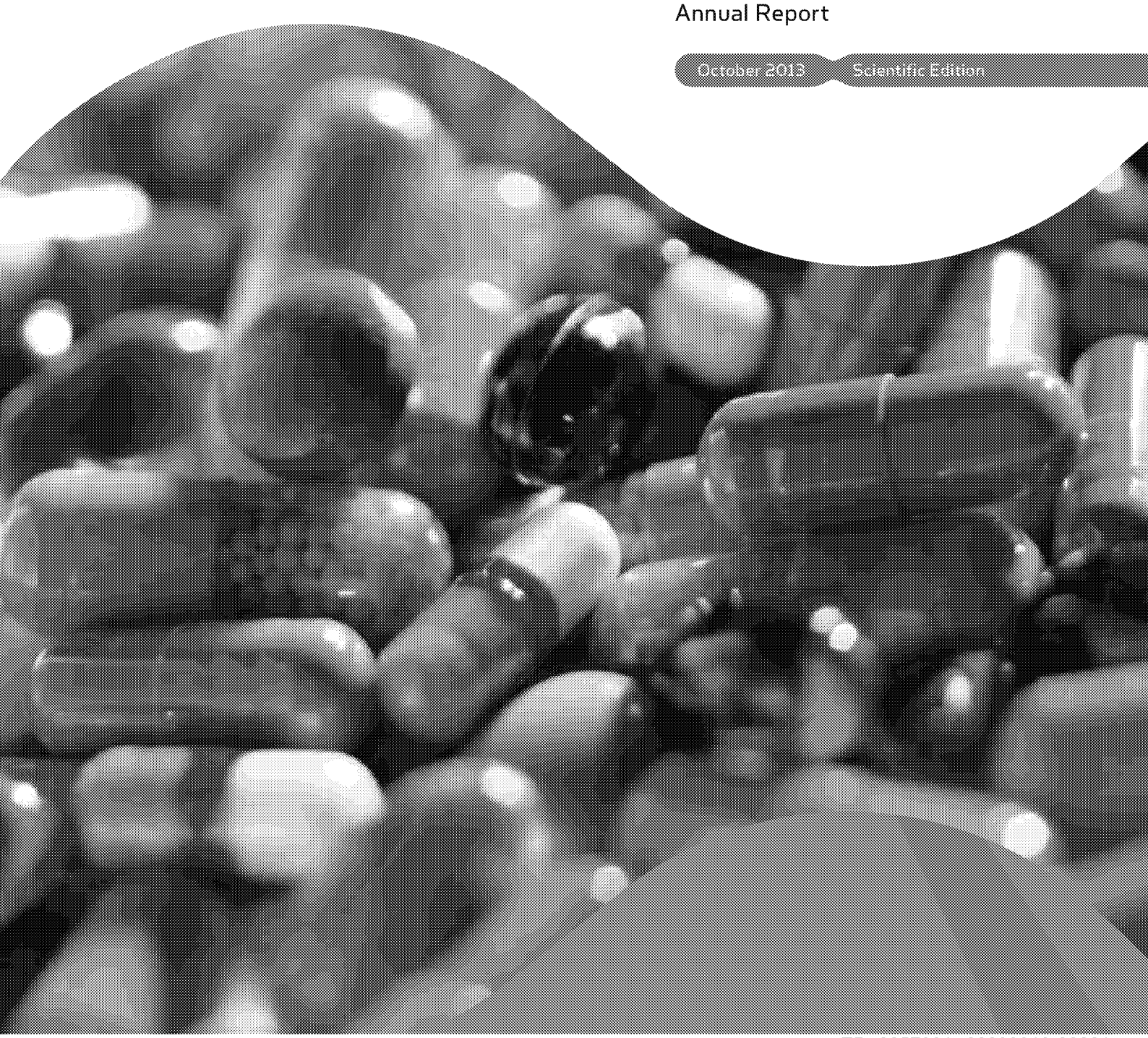
French agency for food, environmental and occupational health & safety

Veterinary Pharmacovigilance

The French pharmacovigilance system and the main events of 2012 in terms of adverse reactions

Annual Report

October 2013 Scientific Edition



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Veterinary Pharmacovigilance

The French pharmacovigilance system and the main events of 2012 in terms of adverse reactions

Annual Report

October 2013 Scientific Edition

Authors: French Agency for Food, Environmental and Occupational Health & Safety (Anses) - French Agency for Veterinary Medicinal Products (ANMV)

Jean-Pierre ORAND, Sylviane LAURENTIE, Elisabeth BEGON, Luc CHARLES, Cédric COLMAR, Eric FRESNAY, Catherine SALLARD, Grégory VERDIER and Gwénaëlle VOISIN

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Abstract

Veterinary medicinal products are only granted marketing authorisation (MA) if an assessment of data on their quality, safety and efficacy shows that the benefits associated with their use outweigh the risks.
The various clinical trials undertaken as part of an MA application may reveal a number of adverse events that are likely to occur following the use of a medicinal product. However, since these trials are conducted in a limited number of animals under standardised conditions of use, the large-scale use of a medicinal product under real-life conditions once it has obtained an MA can further highlight adverse events related to this medicinal product and reveal potential risk factors (species, breed, age, pre-existing conditions, etc.).
Such events are monitored under the national veterinary pharmacovigilance system. Nevertheless, since the applicable regulations governing veterinary medicinal products are European, the surveillance undertaken by Anses-ANMV also occurs within a European framework.
The scope of veterinary pharmacovigilance is very broad since it encompasses:

- the reporting of adverse events in animals after administration of a veterinary medicinal product or a medicinal product for human use in the framework of the 'cascade' approach,
- the reporting of adverse events in humans after administration of a veterinary medicinal product to an animal,
- the collection of information about suspicions of lack of efficacy,
- questions regarding withdrawal periods and residues,
- environmental issues.

The objective of pharmacovigilance is to detect any emerging signs as early as possible, whether these are unexpected adverse events or expected adverse events whose frequency or severity is unexpected, and then to take appropriate risk control measures such as adding a precaution for use or withdrawing a product's marketing authorisation (MA).

MA holders are obliged to establish a pharmacovigilance system that meets their different regulatory requirements, especially in terms of recording, communicating and assessing any adverse events. In France, the companies with this responsibility are pharmaceutical establishments authorised by ANSES-ANMV as veterinary medicinal product distributors specially authorised for this activity, and they are subject to regular controls by ANSES-ANMV inspectors.
To date, 57 establishments have this status of "distributor", and in accordance with the decisions made by the Director General of ANSES concerning frequency of inspections, 12 to 15 sites responsible for pharmacovigilance are inspected annually by the ANMV. This does not include any inspections related to specific events.

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The results of the 2012 inspections show that the pharmacovigilance systems in place are operational. The main areas for further improvement concern the processes relating to organisation of pharmacovigilance systems and quality management.
The number of serious cases reported in France continues to increase steadily. This increase applies to all animal species combined.

Review of adverse events in animals in 2012

In 2012, the ANMV recorded 3,058 cases of adverse events in animals in its national database, 43% of which were regarded as serious. However, to consider them under the same conditions as those of the 2011 report, it is first necessary to subtract the 149 cases of non-serious adverse events for which ANSES-ANMV sought details from the MA holder concerned in order to prepare the press release on SERESTO collars.
Under these conditions there was a slight increase in the number of reported cases compared to the previous year (2,909 cases in 2012 compared with 2,836 in 2011).

This number includes all reports submitted either directly to the authorities, i.e. ANSES-ANMV and the Veterinary Pharmacovigilance Centre in Lyon, or by MA holders electronically to ANSES-ANMV.

Over 90% of the reports submitted to the authorities were sent by veterinary practitioners. Animal owners and breeders submitted 7.57% of all reports.
As in 2011, the vast majority of the adverse events that were reported in 2012 involved companion animals with 82% of reports involving dogs or cats. Cattle accounted for 9.3% of all reports. Other species accounted for less than 2% per species.
The relative weight of the different therapeutic categories involved varied by species. In companion animals, antiparasitics were the primary therapeutic category (43% for dogs and 47% for cats, excluding permethrin). In cattle, vaccines were the leading category (32%).
Rather than particular risk profiles, the above figures reflect significantly higher exposure in these animal populations to certain types of products and/or greater responsiveness on the part of the reporters to events occurring in healthy animals.
The breakdown between serious and non-serious cases varied depending on the therapeutic category: for external and internal antiparasitics, reports mostly concern non-serious cases (75% and 64% respectively). In contrast, for vaccines, non-steroidal anti-inflammatory drugs and antimicrobials, the reports primarily concern serious cases (74%, 65% and 59% respectively).

Pharmacovigilance beyond the scope of strict adverse events

While pharmacovigilance mainly involves adverse events related to veterinary medicinal products in the strict sense, it also concerns suspicions of lack of efficacy, information about potential environmental risks and information about the validity of withdrawal periods for veterinary medicinal products. However, cases of adverse events in animals are clearly dominant since they accounted for 94% of all reports. Suspicions of lack of efficacy accounted for 5.8% of all reports and other cases accounted for less than 1%.

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Adverse events resulting from uses not specified on the Summary of Product Characteristics (SPC)

In a few cases defined by the regulations, a veterinary practitioner can prescribe the use of a medicinal product outside the terms of its MA (off-label use). Of the 3,058 animal cases reported in 2012, 1,028 (34% of reports) involved uses outside the terms defined in the marketing authorisation. The main species involved were cats (54% of reports), dogs (30%) and cattle (5%). This breakdown by species is entirely comparable to the results obtained in 2011, with respectively 52%, 32% and 6% in these three species.

In cats, nearly half of these reports described the use of medicinal products containing permethrin, despite this active substance being formally contraindicated for this species. Permethrin is in fact an antiparasitic authorised for dogs that can cause serious adverse effects and even mortality in cats. The general public was reminded of this information by a press release issued in June 2013.
In dogs, 50% of these reports were related to antiparasitics. For this species, off-label use was most often related to improper dosing (often overdosing).
In cattle, the respective shares of the different therapeutic categories are more balanced, and none stand out as clearly as for domestic carnivores. Overall, reports involving off-label use essentially concern dosing errors and non-compliance with the products' therapeutic indications and/or routes of administration.

The most commonly reported medicinal products involved in serious cases in 2012

Of the 35 veterinary medicinal products involved in at least 10 reports of serious cases in 2012, 27 are authorised exclusively for pets.
In terms of therapeutic category, 16 of the reported medicinal products were vaccines, 10 were antiparasitics and 3 were non-steroidal anti-inflammatory drugs (NSAIDs).
The number of reports of adverse events is only one of the factors used to assess the potential risk related to the use of a medicinal product. It is in fact essential to compare this gross number of cases to the total number of exposed animals over the period in question. This is how incidence is evaluated.
When calculating the incidence of adverse events related to these 35 medicinal products, it appears that incidence remained very low (less than one case per 10,000) for 27 medicinal products, and none of the cases led to an incidence greater than one case per 100 treated animals.
It should also be kept in mind that while incidence is an important parameter in the surveillance of medicinal products, it remains relative considering its calculation method. This is why, in addition to statistical results, the surveillance of a veterinary medicinal product takes into account other factors such as the profile of observed clinical signs in relation to the pharmaco-toxicological profile of the compounds in question, the severity of these signs and changes over time (epiphenomenon or persistence over time).

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Key events in 2012

Exemption from regulation of poisonous substances intended for veterinary medicine

The active substances contained in veterinary medicinal products are, with rare exceptions, classified as poisonous substances on the basis of classifications introduced when the drug is used in humans. This classification in particular affects the rules for issuing the drugs concerned (prescription required, quantity issued, etc.). However, it is also possible, under certain conditions, to exempt these substances from the requirements arising from the poisonous substance classification.

The Ministries of Agriculture and Health decided to revise the existing provisions and the lists of substances or preparations concerned, due to the obsolete nature, therapeutically speaking, of the exempt substances and the benefit of hindsight regarding pharmacovigilance on certain drugs.

Accordingly, the French Agency for Veterinary Medicinal Products was asked to conduct, in conjunction with the French Commission for Veterinary Medicinal Products (CNMV), a scientific assessment of the existing exemptions and those requested by healthcare professionals.

This exercise led to the publication of the Ministerial Order of 24 April 2012 on the exemption from regulation of poisonous substances intended for veterinary medicine, which repealed the Ministerial Order of 20 July 1949 as amended by the Ministerial Order of 3 December 1986.

Intramammary products for non-lactating cows

Following the identification of cases of mortality in cows presenting peracute mastitis that occurred at dry-off after administration of intramammary ointments, ANSES-ANMV asked the CNMV about the conditions for assessing causality in these reports. As a result of this work, the SPC for all products intended for non-lactating cows now provides information on the possible onset of mastitis despite treatment.

Permethrin in cats

Permethrin is an antiparasitic authorised for dogs that can cause serious adverse events and even mortality in cats. This toxicity is related to cats' inability to eliminate certain compounds like permethrin. Affected cats mainly have neurological symptoms (tremors, seizures, ataxia, agitation, hyperaesthesia, coma) with or without digestive symptoms such as hypersalivation.
Although communication initiatives carried out in 2006 and labelling changes have reduced the number of accidents occurring in cats, ANSES-ANMV is still recording reports of adverse events in this species (258 in 2012, of which 121 were regarded as serious).
As a reminder of the toxicity of permethrin-based antiparasitics to cats, ANSES-ANMV issued a new press release in June 2013.

Changes to MAs related to pharmacovigilance data and reported in 2012

The findings from pharmacovigilance data can lead to changes in authorisations for veterinary medicinal products. When the MA has been granted according to the centralised procedure, these decisions are taken by the European Commission (CANILEISH®, COXEVAC®, CERTIFECT®, ATOPICA®).

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With national MAs, these decisions are the responsibility of ANSES-ANMV (FELIGASTRYL®, CALMIVET TABLETS®).

Specific measures taken in 2012

Two press releases issued in July 2012 drew prescribers' attention to two drugs: CLOSAMECTIN POUR-ON SOLUTION FOR CATTLE® and SERESTO® collars, requesting them to report any adverse events.

Adverse events in humans in 2012

Adverse events in humans can occur through contact with treated animals, through direct contact with a veterinary medicinal product during administration to animals, or through mishandling, misuse or abuse of a veterinary medicinal product.
The 435 cases of adverse events that were recorded in 2012 involved at least 228 different veterinary medicinal products. As in 2011, the main therapeutic categories involved were antiparasitics (44%), vaccines (23%) and euthanasia drugs (4%). The remaining reports were divided among the various other therapeutic categories. Excluding reports related to euthanasia drugs, the symptoms described were temporary and relatively benign forms of irritation: primarily skin, eye and/or respiratory signs with external antiparasitics, and inflammatory reactions with accidental injection.

Conclusion

The results of the 2012 assessment show that the total number of reports continues to increase steadily. The results are generally comparable to those obtained in 2011 and confirm that the national system in place is fully capable of detecting new signs and thus supplementing the available knowledge on veterinary medicinal products.

However, the observation made in 2011 about the low level of reporting in certain sectors has been confirmed. For this reason, in addition to its regular assessment activities, ANSES-ANMV held discussions with a view to developing a number of initiatives in terms of communication and promotion of pharmacovigilance in the production animals sectors.

In terms of communication, various studies have been conducted in collaboration with the French Commission for Veterinary Medicinal Products (CNMV). *NB: The different documents (minutes, changes to SPCs, CNMV opinions) are available on the ANSES website.*

Promotion activities in the production animals sectors have also begun (attendance at conferences, changes to reporting models), and thanks to an increase in staff in the Pharmacovigilance Department, will continue (setting up networks, etc.).

For 2013, the priority themes chosen by Anses-ANMV in the field of pharmacovigilance and its stimulation concern the continuation of communication initiatives, and the promotion of reporting in the production animals sectors, including giving primary consideration to both initial and continuing training of veterinarians.

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Besides pharmacovigilance, a special effort is being made to monitor the various impacts of the use of veterinary medicinal products, after they have been placed on the market (post-MA in general). The reorganisation of the ANMV, with the creation of the market surveillance unit, which took place in July 2013, should also optimise the measures taken in this area.

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INTRODUCTION

Veterinary pharmacovigilance involves monitoring reactions to veterinary medicinal products and providing information about the risk of adverse events. The current scope of veterinary pharmacovigilance is very broad since it encompasses:

- the reporting of adverse events in animals after administration of a veterinary medicinal product or, in the highly regulated framework of the 'cascade'[1] approach, a medicinal product for human use,
- the reporting of adverse events in humans after administration of a veterinary medicinal product to an animal,
- the collection of information about suspicions of lack of efficacy,
- issues of withdrawal periods and residues,
- and environmental issues.

Pharmacovigilance includes the recording of the data communicated, their expert appraisal, the assessment of the causality relationship between medicinal products and the observed effects, the evaluation and monitoring of the risk-benefit ratio and, if necessary, the implementation of corrective measures (precautions or restrictions for use, or withdrawal of a medicinal product from the market).

This monitoring activity applies to veterinary medicinal products with a marketing authorisation (MA) issued by Anses-ANMV or a European marketing authorisation issued by the European Commission, veterinary medicinal products with a provisional authorisation for use issued by Anses-ANMV, and autovaccines.

The clinical trials undertaken and assessed in the framework of an MA application for a medicinal product are conducted on a limited number of animals under standardised conditions of use. The MA may mention a number of adverse events that are likely to occur and include precautions for use. However, adverse events to this medicinal product can only be properly assessed further to its large-scale use under real-life conditions.

Indeed, pharmacovigilance, when based on a large number of observations, can better determine the nature and incidence of adverse events and their risk factors (species, breed, age, pre-existing conditions, etc.). The information collected and analysed in this context is used to better inform prescribers and users of the precautions that should be taken and potential risks related to the use of veterinary medicinal products.

[1] Off-label use regulated by the French Public Health Code (L.5143-4), which defines the conditions under which a veterinary practitioner can in exceptional circumstances use a human medicinal product if no veterinary medicinal product is available on the market to treat a diagnosed disease in the species concerned.

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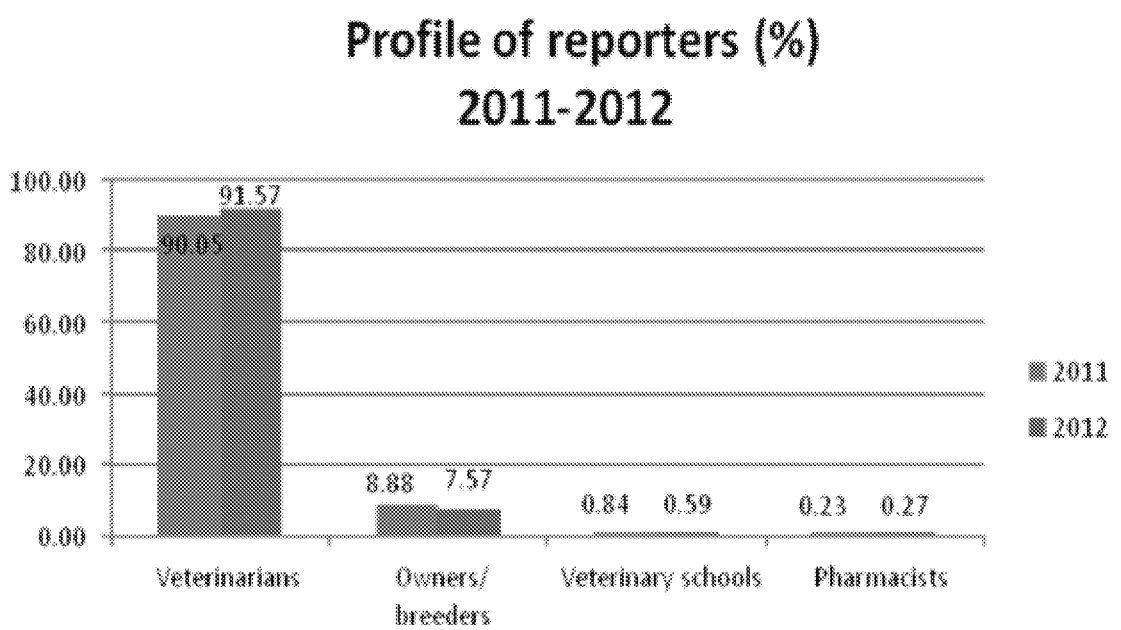
I - THE ORGANISATION OF VETERINARY PHARMACOVIGILANCE

Monitoring of veterinary drugs marketed in France involves various stakeholders (see Annex 1). Its foundation is health professionals, mainly veterinarians, who are in the front line when it comes to characterising the adverse events that arise following the use of veterinary medicinal products.

These health professionals are responsible for the majority of the reporting in France.

Indeed, for the reports sent directly to the authorities, over 90% of reporters are private veterinarians (see graph below). The breakdown by type of reporter in 2012 is quite similar to that observed in the previous year, although there was a very slight decrease in reports from owners and breeders.



These reports are transferred either to the authorities, i.e. Anses-ANMV and the Veterinary Pharmacovigilance Centre in Lyon (CPVL), or to the pharmaceutical companies concerned, the MA holders.

All reports transmitted either to the CPVL or directly to Anses-ANMV are registered in the national database.

Regarding the reports sent to the MA holders, they have a regulatory requirement to transmit reports of all serious cases occurring in France to Anses-ANMV, by electronic means, within 15 days. However, at present, this requirement to transmit reports as they come in does not apply to non-serious cases. Although these are also saved and analysed by the MA holders, they are only

Serious cases in animals

When occurring in an animal, a serious adverse event is an adverse event that results in permanent or prolonged symptoms resulting in a congenital anomaly or malformation, major disability or incapacity, may be life-threatening or even result in the death of the treated animal.

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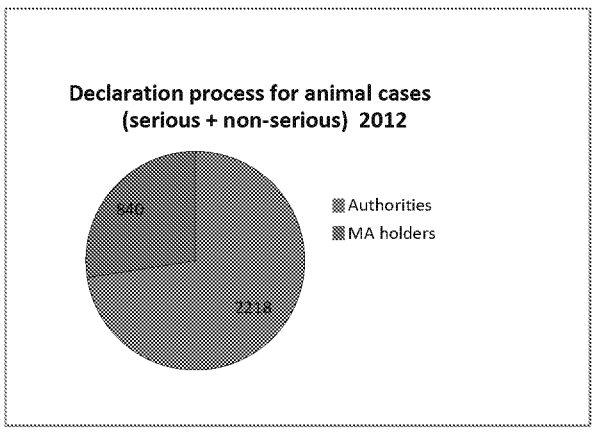
brought to the attention of ANSES-ANMV when the MA holders submit their periodic safety update reports (PSURs). These PSURs provide a summary of the cases (serious and non-serious cases collected and analysed by the MA holder) and are transmitted according to a schedule defined by the regulations. Thus, non-serious cases may only be brought to the attention of ANSES-ANMV as much as three years after they occur.

For the purposes of this document, for reports transmitted by MA holders, only those transmitted electronically have been taken into account.



In 2012, 72.5% of the reports recorded in the national database had been sent to the authorities: ANSES-ANMV and the CPVL. This breakdown between authorities and MA holders is comparable to that observed in 2011 (76%).

In France, the reporting model is determined by a decision of the Director General of ANSES. There are currently three systems available for reporters to transmit these reports to the authorities:

- printing out and posting the reporting forms that are available on the websites of both ANSES (http://www.Ansespro.fr/notificationMV/) and the CPVL (http://www2.vetagro-sup.fr/serv/p_doc/pdf/fiche_animal02.pdf)
- telephoning the CPVL, open 24h a day. Following this telephone call, the CPVL sends the reporter a pre-filled report form that should be completed and returned to the CPVL.
- electronic submission via the ANSES website (http://www.Ansespro.fr/notificationMV/). This portal for the electronic submission of adverse events was first made available to reporters in February 2010. When a report is sent, the system automatically sends an acknowledgment to the reporter.

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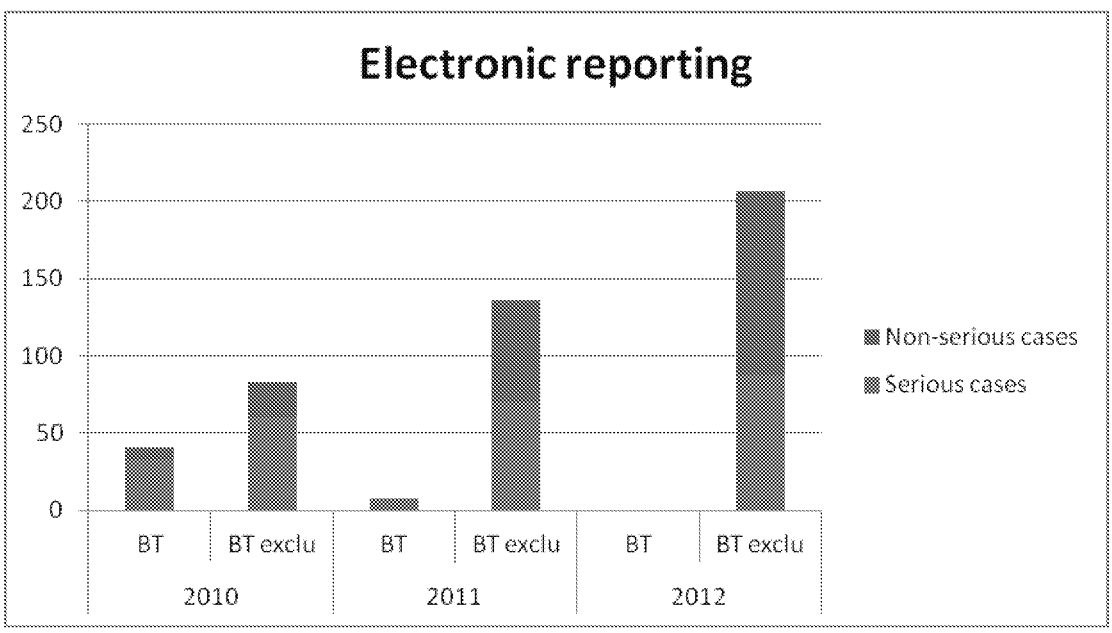
This portal was initially set up as part of the bluetongue vaccination campaign (see Section II). The figure below shows that it has always also been used to report adverse events occurring following the use of drugs other than vaccines against bluetongue. Moreover, each year around a hundred additional reports are sent to ANSES-ANMV through this portal. These relate to both serious (42% in 2012) and non-serious cases.



Each report undergoes an individual expert appraisal and all of the reports are used to conduct an overall expert appraisal.
Marketing authorisation holders have a regulatory requirement to monitor adverse events occurring following the use of their medicinal products.
The mission of ANSES-ANMV, as the competent authority, is to oversee all veterinary medicinal products marketed in France.
It also monitors the pharmacovigilance systems established by the MA holders, for French companies, through on-site inspections.

I – 1 Expert appraisal of adverse events reports

Individual expert appraisal

Each report recorded in the national database undergoes an individual appraisal by ANSES-ANMV or the CPVL.

This individual appraisal is performed by one of the three experts from the ANSES-ANMV Pharmacovigilance Department, or one of the three CPVL experts, who are all veterinarians. It draws on all the information provided in the report, as well as on the available knowledge on the drug(s) involved and the corresponding active ingredients: data from the Summary of Product Characteristics (SPC), pharmaco-toxicological knowledge, scientific bibliographic data, and pharmacovigilance data already collected (similar cases recorded in the national database). This expert appraisal leads to a causality assessment being defined for each of the drugs mentioned in the report, according to the ABON system (see Annex 2), which characterises the probability of a causal link between the drug and the adverse event.

This causality rating, accompanied by a conclusion summarising the underlying reasoning, is (for reports that were initially transmitted to ANSES-ANMV or the CPVL) sent to the initial reporter via a response letter addressed to them personally.

The causality rating reflects at a time "t" the estimated strength of the causal link between a drug and an adverse event. The method used in veterinary pharmacovigilance for determining causality evolved at European level during the course of 2012, with Category "O" being subdivided into O (unclassifiable/unassessable) and O1 (inconclusive). This method is described in Annex 2 of the report.

This rating is subject to change, to keep pace with developments in knowledge of the drugs and information relating to the report (receipt of additional test results, for example). A large proportion of cases received are ranked as "O" or "O1", corresponding to situations where no conclusion can be drawn about the potential link between the drug and the event, either due to a lack of information in the report, or because it concerns an unexpected effect. Thus, although an "O" or "O1" rating for an individual report may seem frustrating in the eyes of the reporter, it must be borne in mind that most signals are likely to emerge from these reports.

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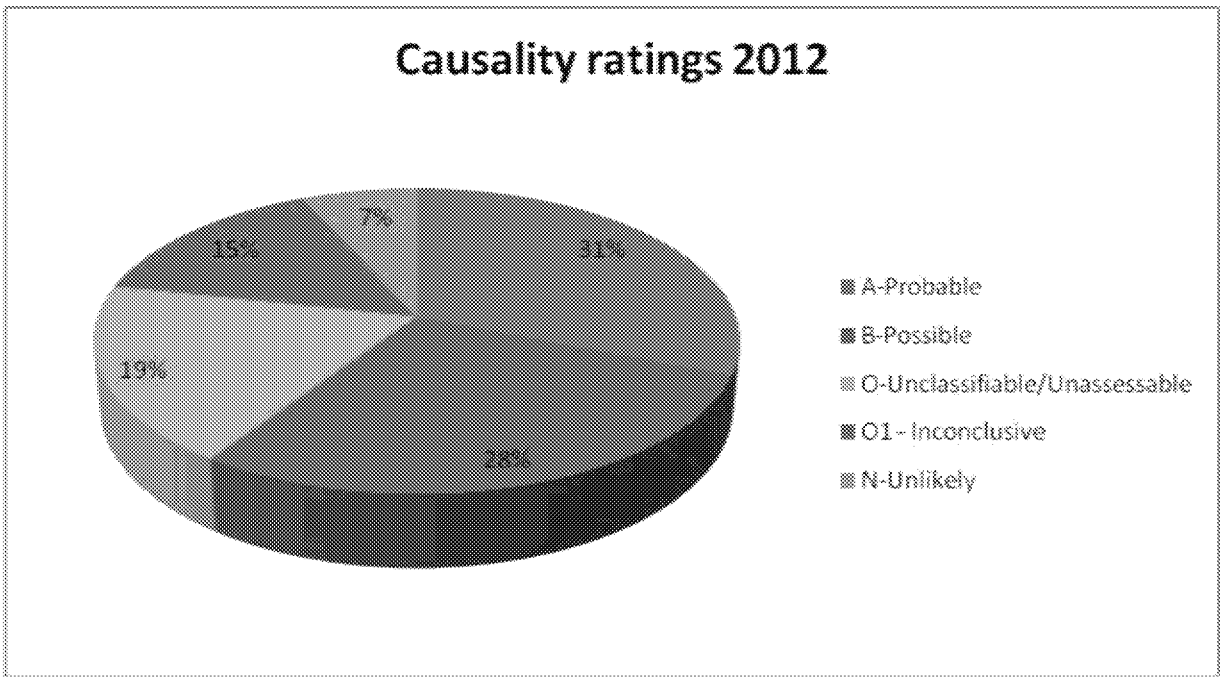
Categories A and B, which correspond primarily to already known adverse events, accounted for 59% of reports in 2012. This is the same proportion as that recorded in 2011.



Categories O and O1 accounted for 34% of reports, as in 2011. The breakdown of categories in 2011 was therefore strictly identical to that observed in 2012.

The risk-benefit ratio is assessed by taking into account all the A, B and O/O1 reports that enable the detection of new adverse events or new aspects of already known adverse events (in terms of frequency , severity, etc.) that can be grouped under the term "signal".

Overall expert appraisal

The individual assessment of reports is a key step in detecting signals, as when each new report is received, the entire database is searched for similar cases. It is supplemented by a review of all of the reports, what could be called an “overall appraisal”, whose methodology is different because it is a statistical analysis of a large number of reports. This so-called "overall" appraisal can take place at different times: when reviewing periodic safety update reports (which summarise all reports received for a given drug over a period ranging from 6 months to 3 years), assessing applications for renewal of MA (when pharmacovigilance data collected for the drug over a period of 5 years are assessed) or following other external requests (for example, a complaint from a veterinarian about one or more drugs).

These two approaches, individual and overall expert appraisal, are complementary for signal detection.

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The internal appraisal conducted by ANSES-ANMV and the CPVL is supplemented by an external expert appraisal, conducted at national level by the experts of the French Commission for Veterinary Medicinal Products (CNMV), and at European level by the Pharmacovigilance Working Party (PhVWP-V) of the European Medicines Agency.

This external expert appraisal can enable a signal to be confirmed or refuted at national or European level. These external experts may themselves be able to add new signals. The exchanges therefore work in both directions.

At national level, at each meeting of the CNMV, a pharmacovigilance session is led by experts from the ANSES-ANMV Pharmacovigilance Department. On this occasion, the serious cases received by the ANMV since the last meeting are reviewed. ANSES-ANMV may also ask the CNMV experts about any other subject. Similarly, the experts from the CNMV can alert ANSES-ANMV about an individual drug and ask them for further analysis on any aspect. These discussions enrich and complement the internal expert appraisal carried out by ANSES-ANMV and the CPVL.

EMA's European working groups, especially the PhVWP-V, also act as forums for exchanges between Member States of the European Union on issues relating to pharmacovigilance. Physical meetings (bi-monthly) are supplemented by electronic information exchange systems (the "Rapid Alert System" and "Non-Urgent Information System"), which enable Member States to stay informed and call on each other when necessary. This provides further input for the internal expert appraisal conducted at ANSES-ANMV and the CPVL.

I – 2 Inspection of veterinary pharmacovigilance activities

ANSES-ANMV is also responsible for enforcing application of the regulatory provisions in the field of veterinary pharmacovigilance.

This mainly involves conducting inspections of veterinary pharmaceutical establishments that engage in pharmacovigilance activities.

The establishments concerned

Monitoring of unexpected adverse events or pharmacovigilance of veterinary medicinal products is carried out by the establishments responsible for placing the product on the market. The entity in charge of doing so is either the MA holder distributing its drug in France from a country in the European Union, or an establishment based in France. In the latter case, the pharmaceutical company then has the status of veterinary medicinal product "distributor" specially authorised for this activity.

Alongside their pharmacovigilance activities, these pharmaceutical companies are generally in charge of advertising, marketing, distribution, batch monitoring, claims and batch recalls, for which they are also inspected.

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Pharmacovigilance activities also involve establishments:

- that prepare autovaccines,
- with a parallel import authorisation,
- responsible for the marketing of homeopathic medicines subject to registration.

In 2012, the ANMV therefore inspects 57 establishments with such "distributor" status. Among these, 20 organisations also have the status of veterinary medicinal product manufacturer.

In accordance with the decisions made by the Director General of ANSES concerning frequency of inspections, 12 to 15 sites responsible for pharmacovigilance are inspected annually by the ANMV. Planning is adapted according to the risk analyses prepared after each inspection.

Inspection objectives and reference standards

Since pharmacovigilance inspections began in 2004, the reference standards have changed:

- First inspection cycle (2004-2006): awareness of GMP[2]-GDP[3] and the French Public Health Code (CSP),
- Second inspection cycle (2007-2009): GMP-GDP-CSP and awareness of volume 9,
- Third inspection cycle (2010-2013): GMP-GDP-CSP-vol 9B[4] and awareness of volume 9B,
- Fourth inspection cycle (2013-2016): GMP-GDP-CSP-vol 9B.

The main aims of inspection are to:

- determine which personnel, resources, systems and facilities have been deployed by the "distributor" to meet the pharmacovigilance requirements,
- identify, record and report any nonconformities that may pose a risk to public health.

Type of inspections

The term "pharmacovigilance inspection" comprises several types of inspection:

- System or product inspection,
- Routine or follow-up inspection,
- Overall inspection or inspection focused on a subject or process,
- National (ANSES-ANMV) or European inspection (on behalf of EMA).

Duration of inspections

The duration of the pharmacovigilance inspections varies depending on:

- The type of inspection,
- The size of the operator and the number of MAs managed,
- The composition of the inspection team (inspectors + experts).

When inspecting the systems set up by these "distributors", inspectors may spend a quarter of their time on an overall assessment of how the pharmacovigilance activities are organised.

[2] Good manufacturing practice
[3] Good distribution practice
[4] Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use

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The pharmacovigilance inspections conducted at the request of the EMA take place over a longer period, lasting up to three days. In this case, the inspections are primarily focused on the pharmacovigilance system for one or more specific MAs.

Use of inspection results

Each inspection is described in a report that, at the end of the adversarial process, enables the Director of the ANMV to rule on the level of compliance of the establishment's activities according to the applicable standards.

The data presented below are analysed statistically, focusing on deviations identified in all the reports from 2012. For the purposes of the current programme, the analysis seeks to identify the main deviations in order to determine the risks associated with this activity.

2012 review

Quantitative data

The ANMV conducted twelve pharmacovigilance inspections in 2012. In terms of planning, eight establishment inspections were scheduled according to the regulatory frequency, three follow-up inspections took place earlier than scheduled for verification, and one pharmacovigilance inspection was carried out at the request of the EMA (centralised procedures).

Figure 1: Changes in pharmacovigilance inspections carried out by ANSES-ANMV over the period 2010-2012

Year	2010	2011	2012
PhV inspections	14	13	12
CVMP inspections included in above total	0	1	1

The inspections show that the pharmacovigilance systems are well established among the MA "distributors", although there is still room for progress.

In 2012, 36 deviations were noted in the field of pharmacovigilance. The main unsatisfactory areas concerned the processes relating to quality management, risk management and organisation of pharmacovigilance.

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Figure 2: Classification of deviations noted during the pharmacovigilance inspections in 2012

Inspected pharmacovigilance processes	No. of discrepancies
Process related to the organisation of PHV	**11**
Contracts	4
Training	4
Interaction with other entities	2
Interaction with subsidiaries	1
Process related to quality and risk management	**10**
Documentation – elements of the quality system/procedure	9
Self-inspection	1
Process related to regulatory obligations of RPHV	**6**
Supervision of the pharmacovigilance system	3
Responsibilities	2
Designation	1
Process related to the PSUR	4
Management of PSURs	3
Monitoring compliance in submission of PSURs	1
Process related to the management of adverse reactions	**3**
Monitoring compliance in reporting of serious cases	2
Management of adverse reactions	1
Process related to the management of pharmacovigilance data	**2**
Management of physical data	1
Management of electronic data	1
Total deviations for 2012	**36**

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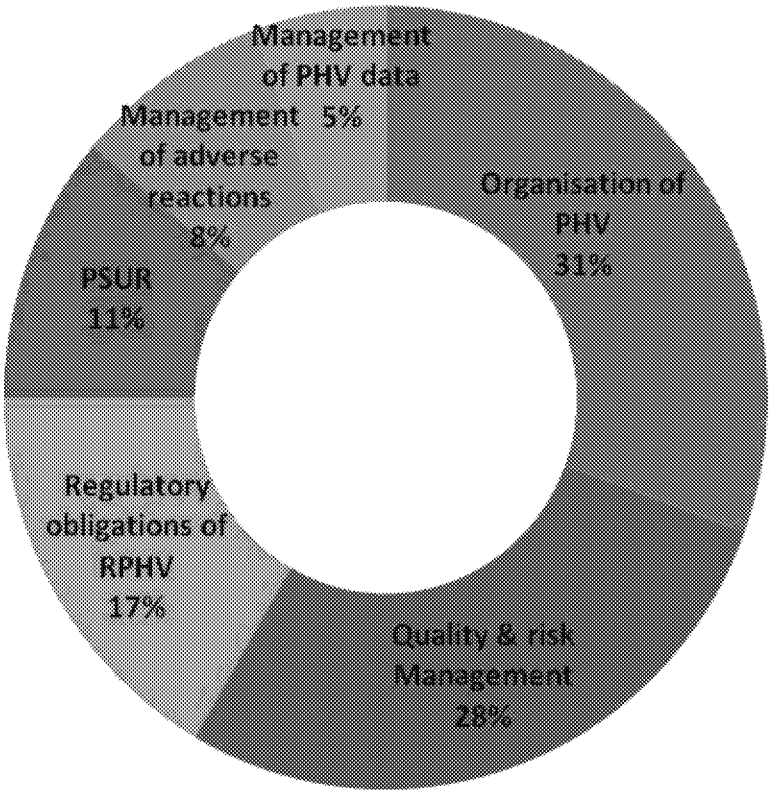
Figure 3: Frequency of deviations noted in 2012 by major pharmacovigilance process



Analysis and summary of deficiencies noted

The inspectors noted some shortcomings in the quality management system, particularly in the pharmacovigilance system procedures (9 deviations) and in the performance of internal audits and quality control operations relating to pharmacovigilance activities (1 deviation). These shortcomings could potentially lead to non-harmonised and uncontrolled practices within the pharmacovigilance system. It should be recalled that, in this context, this could alter the quality of the pharmacovigilance data, leading to delayed detection of a possible change in the risk/benefit ratio of a veterinary drug.

A detailed analysis of the deviations also revealed failures relating to the staff in the pharmacovigilance system. Firstly, deficiencies relating to shortcomings in the establishment organisation charts, job descriptions and delegation of responsibilities (6 discrepancies) may prevent the head of pharmacovigilance from guaranteeing effective supervision of the "distributor's" pharmacovigilance system.

Secondly, the absence, inadequacy or non-assessment of training provided to staff likely to be involved at different levels in the pharmacovigilance system (4 deviations) reflects a certain degree of non-proficiency in the process of acquisition and consolidation of knowledge and know-how that is essential to the implementation of veterinary pharmacovigilance within pharmaceutical companies.

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Lastly, the inspectors found shortcomings in the contractual arrangements relating to pharmacovigilance activities. These relate to pharmacovigilance activities divided between two pharmaceutical companies responsible for placing the same product on the market (4 deviations). These inadequacies, mainly concerning formalisation of the respective responsibilities of each party involved and the way in which pharmacovigilance data is shared, may make it difficult for these establishments to meet their obligations with regard to pharmacovigilance.

International activities

The inspection unit has a representative on the European Pharmacovigilance Inspectors Working Group set up by the EMA. The group's main task is to harmonise and coordinate activities related to pharmacovigilance and inspection at EU level. Each member is involved in the preparation of guidelines and procedures for inspection and pharmacovigilance, and plays a key role in developing collaborative projects within the EU.

At the same time, the EMA draws on the inspection unit's expertise to carry out pharmacovigilance inspections of MA holders based in France or Europe for products authorised via the centralised procedure.

In 2008 the ANMV also joined the Pharmaceutical Inspection Cooperation Scheme (PIC/S), an organisation of 41 authorities whose main objectives are to develop recommendations for good practice in the pharmaceutical field. The PIC/S has plans to extend its mandate and sphere of competence to good pharmacovigilance practice and good clinical practice, through the creation of an ad-hoc working group.

Outlook for 2013

For 2013, the main objectives for the pharmacovigilance inspections are to ensure compliance with the frequency of inspections, to assess compliance with volume 9B and shortly with the French good veterinary pharmacovigilance practice guidelines being developed, and to ramp up inspections at the request of the CVMP.

In addition, during the inspections, particular attention will be paid to the measures implemented by distributors relating to the following two themes:

- effective retrieval of reports transmitted by the ANMV from EudraVigilance,
- registration of compensation claims for harm to an animal as a result of a pharmacovigilance case.

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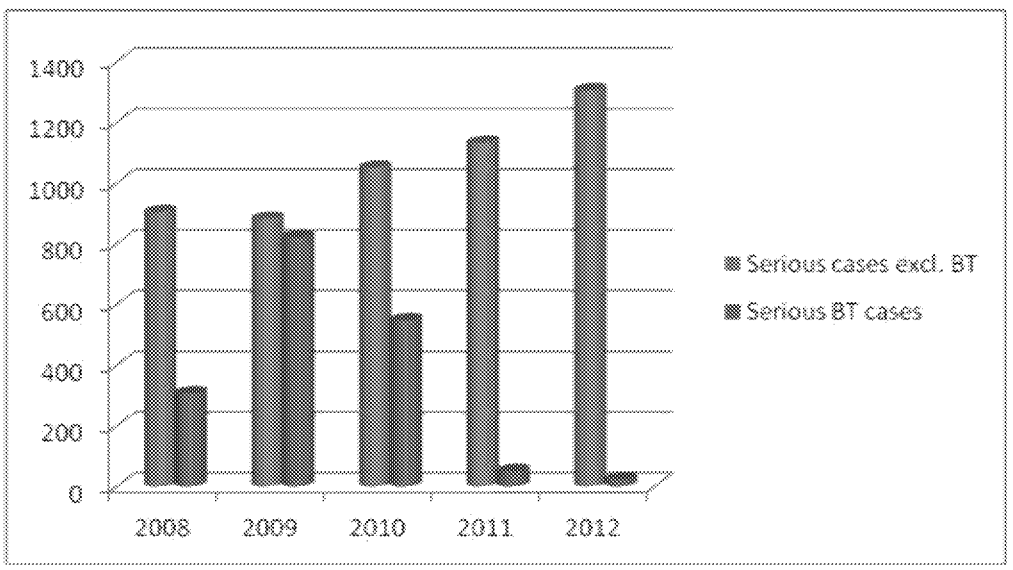
II - CHANGES IN THE NUMBER OF SERIOUS CASES OVER THE PAST 5 YEARS

The following graph shows the changes in the total number of **serious** adverse events occurring in animals as reported over the past five years. The data correspond to the number of reports of serious adverse events occurring in animals following administration of a veterinary medicinal product or a medicinal product for human use in the framework of the 'cascade' approach.

Serious cases connected with the vaccination against bluetongue have been recorded separately. This was an epiphenomenon that is now almost over, since in 2012, only 22 serious cases were reported following administration of vaccines against bluetongue *(see the pharmacovigilance annual report for 2011*).

However, unlike in the previous report, serious cases occurring in cats related to the administration of permethrin (an external antiparasitic), which continued to be reported, have been included in the overall number.



The number of serious cases (excluding bluetongue, BT) has risen steadily since 2009, with an average increase of 14% each year. In 2008, the number of serious cases was slightly higher than in 2009 due to the increase in cases of permethrin in cats that year.

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III - ADVERSE EVENTS IN ANIMALS IN 2012

Compared to 2011, 222 additional reports were recorded in 2012. However, to compare the two years under the same conditions, only 73 additional reports should be taken into account. This is because, in order to prepare the press release on SERESTO collars (see Section V-3), ANSES-ANMV asked the MA holder concerned to forward details of all the non-serious cases it had recorded. This meant that 149 non-serious cases, which would only have been brought to the attention of ANSES-ANMV subsequently through the PSURs, were also recorded in 2012.
The number of reports submitted in 2012 was therefore slightly higher than in 2011. However, the breakdown between serious and non-serious cases was exactly the same in both years.

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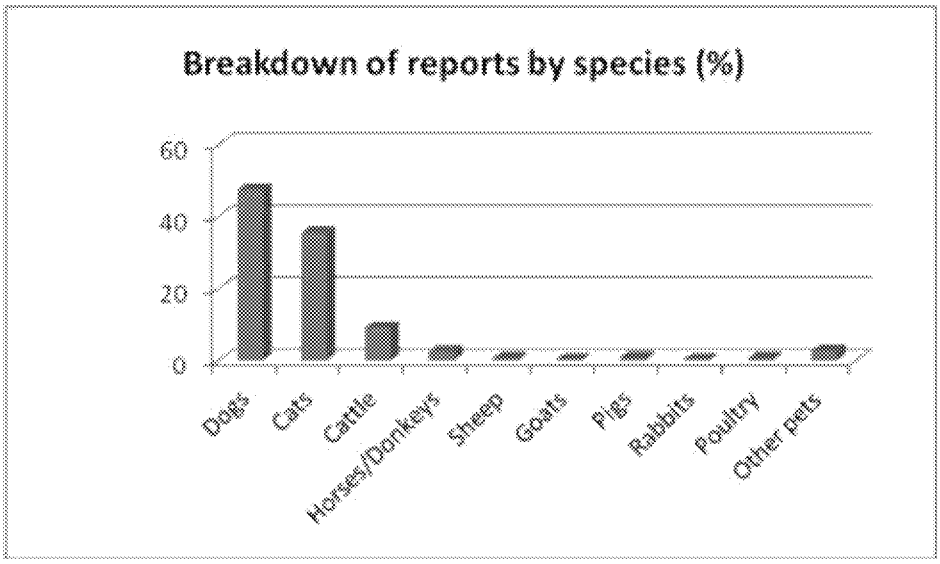
III - 1 BREAKDOWN OF CASES BY SPECIES

As in 2011, the vast majority of the adverse events reported in 2012 involved domestic carnivores, with 82% of reports involving dogs or cats. Cattle accounted for just under 10% of all reports.
Other species accounted for less than 3% per species.



III - 2 BREAKDOWN OF REPORTED ADVERSE EVENTS BY SPECIES AND THERAPEUTIC CATEGORY

A single report may concern several medicinal products and each medicinal product belongs to a therapeutic category. This explains why, in 2012, 3764 medicinal products were mentioned in the 3058 reports collected for animals. A breakdown of adverse events by species and therapeutic category(ies) for the medicinal products mentioned in these reports is given below.

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	Dogs	Cats	Cattle	Horses/ Donkeys	Sheep	Goats	Pigs	Rabbits	Poultry	Other pets/ Wildlife	TOTAL
External antiparasitics	495	535	5	4	1	0	0	0	5	36	1081
Internal antiparasitics	235	254	86	23	9	4	0	0	8	14	633
Antimicrobials	133	92	79	15	2	5	0	0	4	2	332
Non-steroidal anti-inflammatory drugs (NSAIDs)	123	55	14	7	1	0	0	0	0	3	203
Vaccines	350	148	107	24	11	3	28	7	4	33	715
Nervous system /Anaesthetics	128	105	15	10	0	0	0	0	0	2	260
Digestive system	63	38	17	6	0	1	0	1	0	4	130
Hormones	56	18	4	2	0	0	0	1	0	3	85
Genital & reproductive organs	48	17	4	0	0	0	0	1	0	0	70
Cardiovascular & circulatory system	47	12	3	1	0	0	0	0	0	0	63
Dermatology	35	19	1	1	0	0	0	0	1	2	59
Others	*74*	*46*	*8*	*1*	*0*	*0*	*1*	*0*	*0*	*3*	*133*
TOTAL	**1787**	**1340**	**343**	**94**	**24**	**13**	**29**	**10**	**22**	**102**	**3764**

Reports involving rabbits were divided between cases occurring in industrial facilities ('rabbits' column) and cases occurring in domestic rabbits ('exotic pets' column).

The main therapeutic categories mentioned in the pharmacovigilance reports are listed in the table above. Regarding the drugs grouped in the "other" category, they overwhelmingly relate to ear drops and ointments, immunomodulatory products or vitamins.
It should be noted that since certain types of medicinal products are frequently used in combination (e.g. anaesthetics and certain vaccines), the total percentages for their categories are considerably increased.

In terms of breakdown between serious and non-serious cases, the graph below shows that for external antiparasitics, 75% of reports were classified as non-serious. The main clinical signs reported were primarily of three types:

- Gastrointestinal (vomiting, anorexia, hypersalivation, diarrhoea, etc.), especially in the event of accidental ingestion of the product, usually by licking;
- Neurological (tremors, lethargy, hyperactivity, dilated pupils, etc.), related to these products' mechanism of action;
- Local reactions at the application site (erythema, pruritus, depilation, etc.) in the event of intolerance to the product in some animals.

For internal antiparasitics, 64% of reports were classified as non-serious. As above, the main associated symptoms were neurological (ataxia, lethargy, tremors, etc.) and/or gastrointestinal disorders (vomiting, diarrhoea, anorexia, hypersalivation, etc.).

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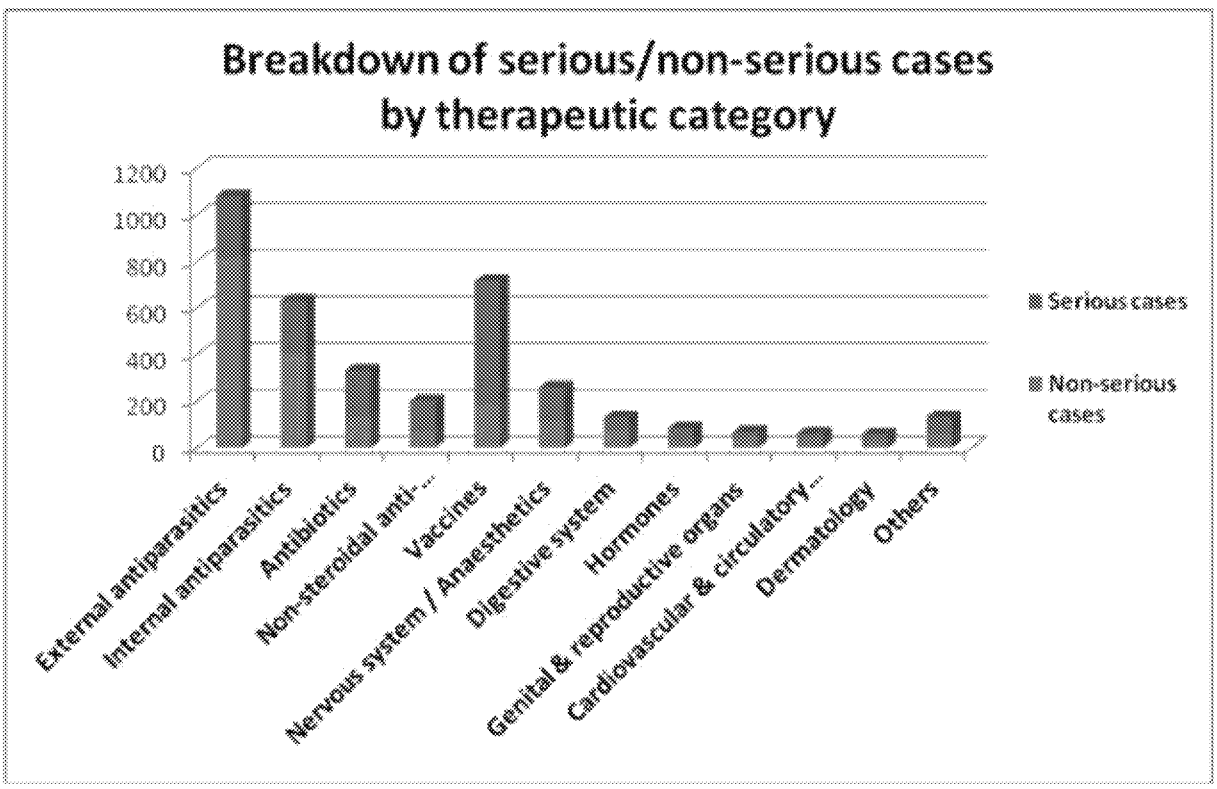
In contrast, for vaccines, 74% of recorded cases were serious. They mainly concerned post-vaccination febrile reactions (lethargy, hyperthermia, etc.) and/or hypersensitivity (allergic oedema, vomiting, diarrhoea). Several cases of anaphylactic reactions led to the death of the animals.

Similarly, for non-steroidal anti-inflammatory drugs, 65% of cases were serious. They mainly concerned gastrointestinal (vomiting, gastro-duodenal ulcers), kidney and liver disorders, as well as some cases of anaphylaxis.

Lastly, for antimicrobials, 59% of reports were serious. Again, the main signs described were hypersensitivity reactions (vomiting, respiratory disorders, ulcers, tremors, etc.), with several cases of mortality.



Compared to 2011, the main change was an increase in the number of reports following the use of external antiparasitics (+8%) along with a slight decrease in reports related to vaccines (-2.5%) and nervous system medicines and anaesthetics (-2.3%).

This change should be considered alongside that in the veterinary medicinal products market itself. According to figures published by the AIEMV (French Industry Association for the Study of Veterinary Medicinal Products), insecticides and external antiparasitics are the categories that experienced the highest growth in market terms between 2011 and 2012 (just under 10%, while average growth in the overall veterinary medicinal products market was around 4%).

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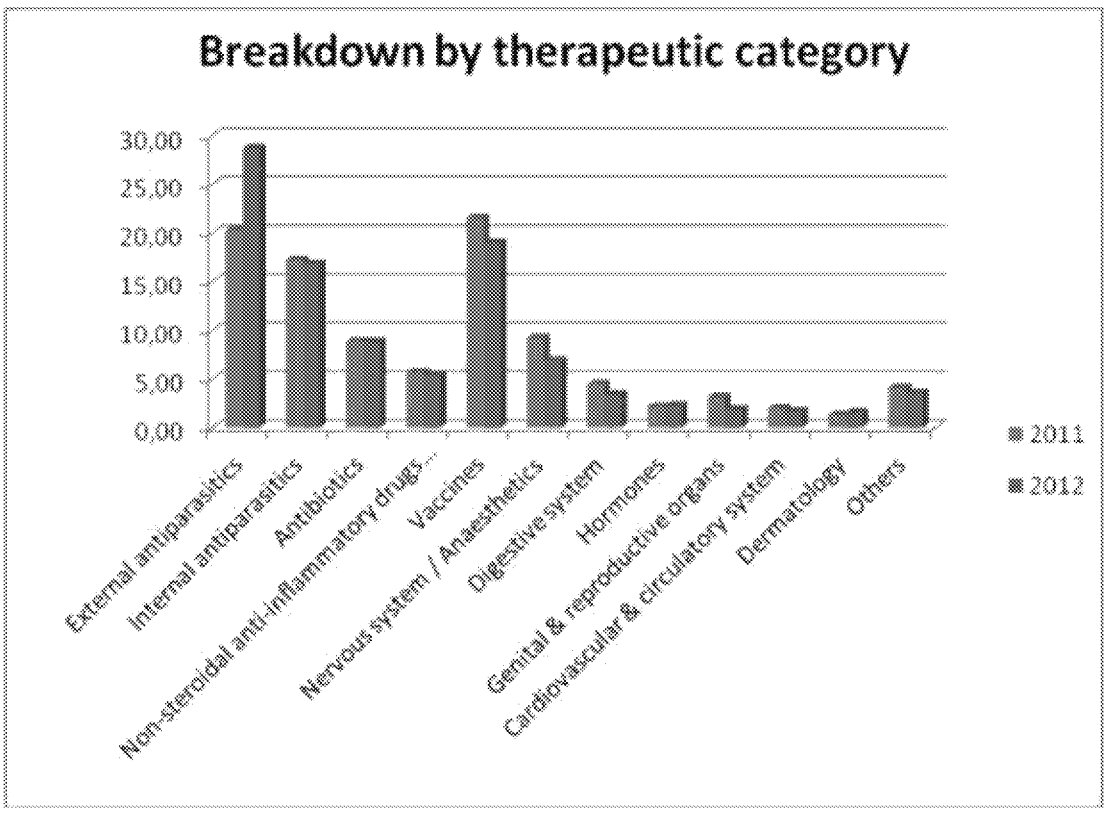

Concerning autovaccines, which in France are included in the scope of pharmacovigilance in the same way as other drugs, just one report was recorded in 2012, describing a local reaction (swelling) at the injection site in a dog.

III – 3 ANALYSIS OF REPORTED ADVERSE EVENTS BY THERAPEUTIC CATEGORY OF MEDICINAL PRODUCT AND BY SPECIES

III.3.a - Dogs

In 2012, in dogs, the collected reports were mainly related to external antiparasitics (29%), vaccines (20%) and internal antiparasitics (14%). The other therapeutic categories each accounted for less than 10% of reports.

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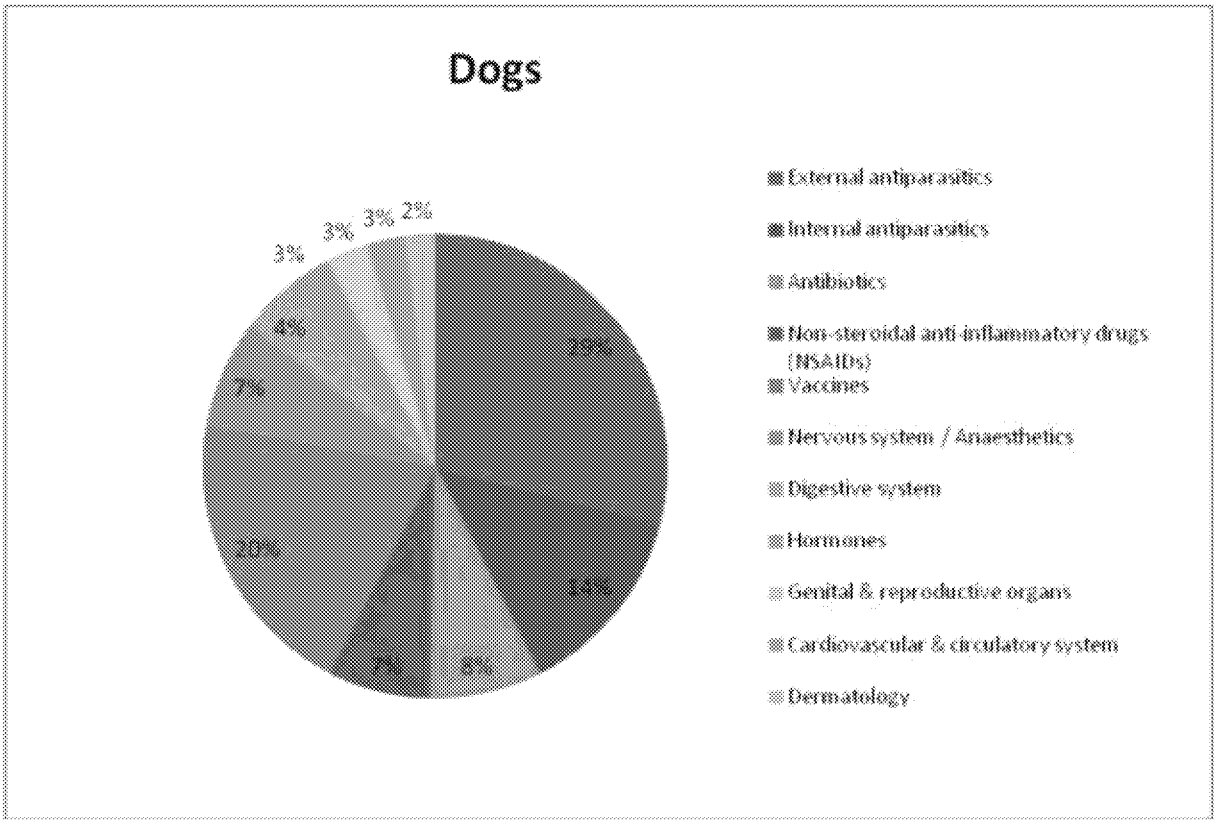

Regarding the breakdown between serious and non-serious cases, 58% of reports related to non-serious cases.

For this species, 86% of cases relating to external antiparasitics were classified as non-serious. For the other therapeutic categories, the observed breakdown between serious and non-serious cases was similar to that obtained for all species combined.

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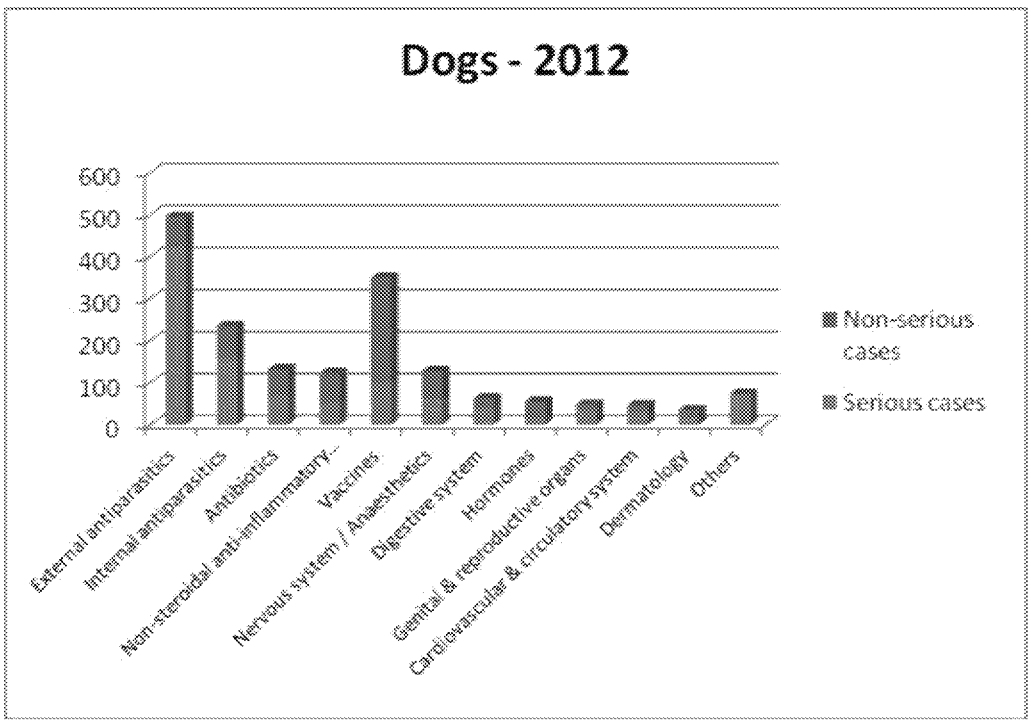

In terms of clinical profile, the described effects were mostly consistent with the general analysis offered above by therapeutic categories: gastrointestinal (vomiting, hypersalivation, diarrhoea, etc.) and nervous symptoms (tremor, ataxia, hyperactivity, etc.) for antiparasitics, and febrile (lethargy, fever, anorexia, etc.) and/or hypersensitivity reactions to vaccines. Local reactions at the administration site were also described fairly regularly for products for external use (external antiparasitics) or vaccines (inflammation at the injection site, itching).

Compared to 2011, there was a sharp increase in reports concerning external antiparasitics (18% in 2011 against 29% in 2012) but a decrease in cases related to internal antiparasitics (18% in 2011 against 14% in 2012) and agents acting on the nervous system – primarily anaesthetics (10% in 2011 against 7% in 2012).

This change partly reflects the overall evolution of the veterinary drug market in France (described previously). In addition, as part of the investigation conducted in 2012 into adverse events from SERESTO collars, the MA holder submitted a series of non-serious cases (which would normally not have been reported immediately to the ANMV), which resulted in a methodological bias (see Section III – 4).

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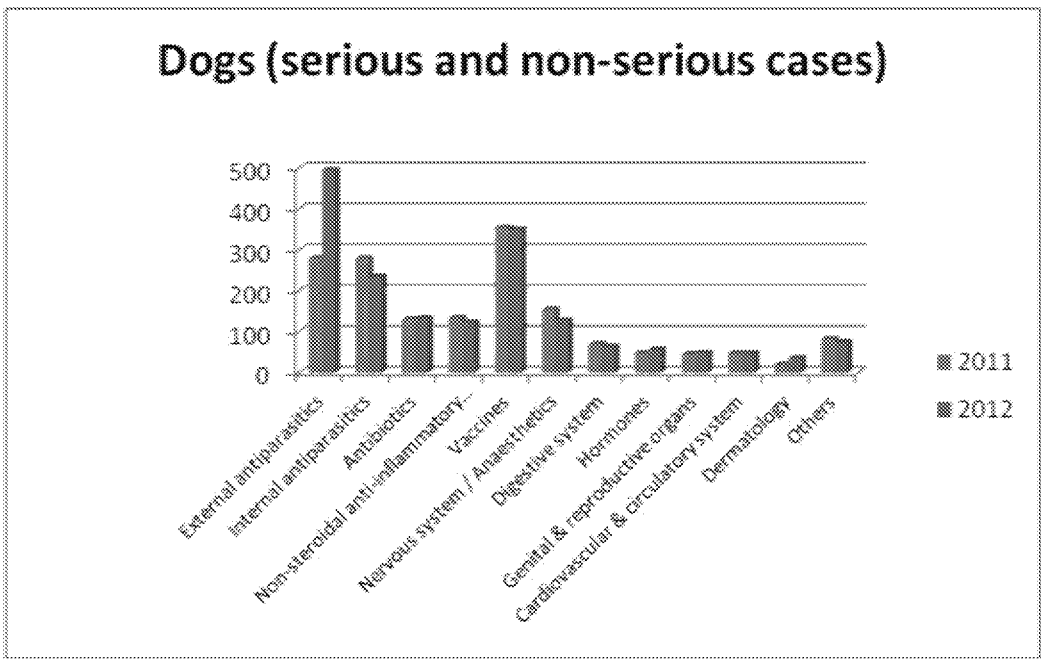
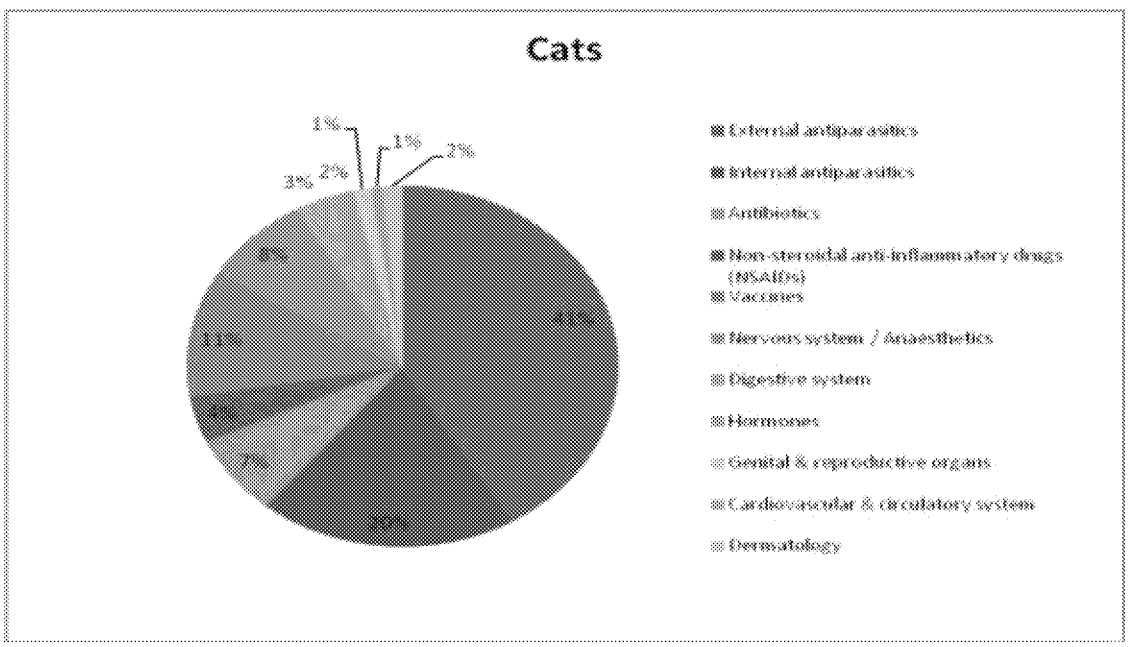


III.3.b - Cats

In cats, external antiparasitics accounted for 41% of reports and internal antiparasitics 20%. Vaccines were involved in 11% of cases. As for dogs, the other therapeutic categories each accounted for less than 10% of reports.



The breakdown between serious and non-serious cases by therapeutic category was similar to that observed for other species, except for the category of external antiparasitics, for which 31% of cases were serious in this species. The main factor explaining this difference relates to the many cases of poisoning occurring in cats following the use of medicinal products containing permethrin intended for dogs. In fact, this substance is extremely toxic to cats, causing convulsions that can be fatal.

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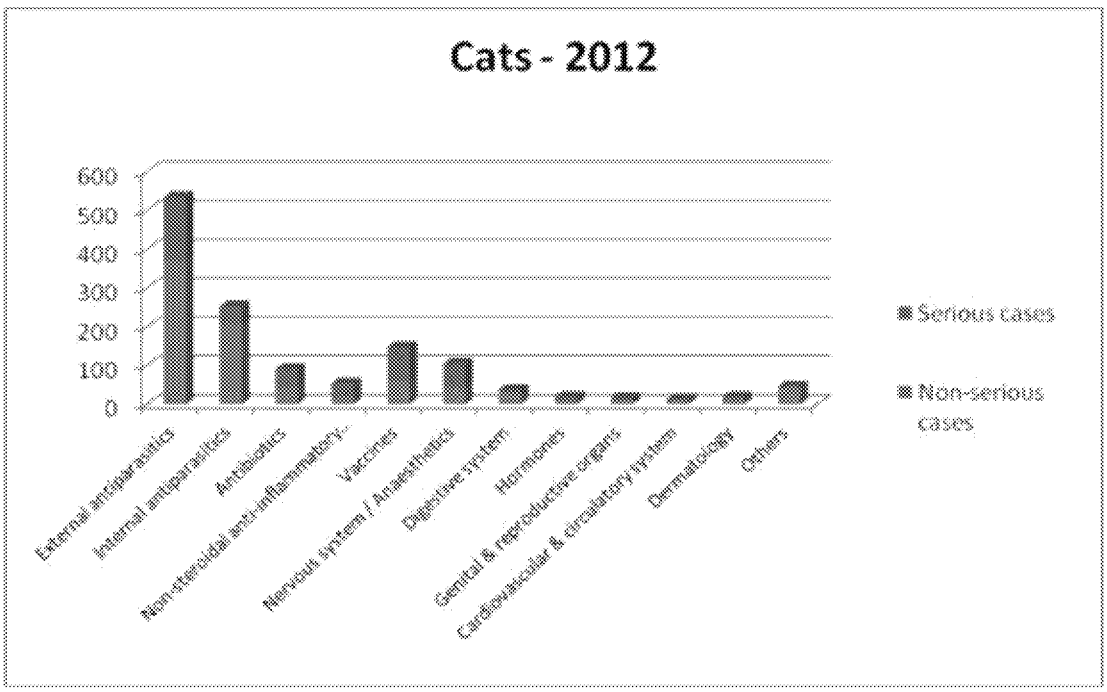
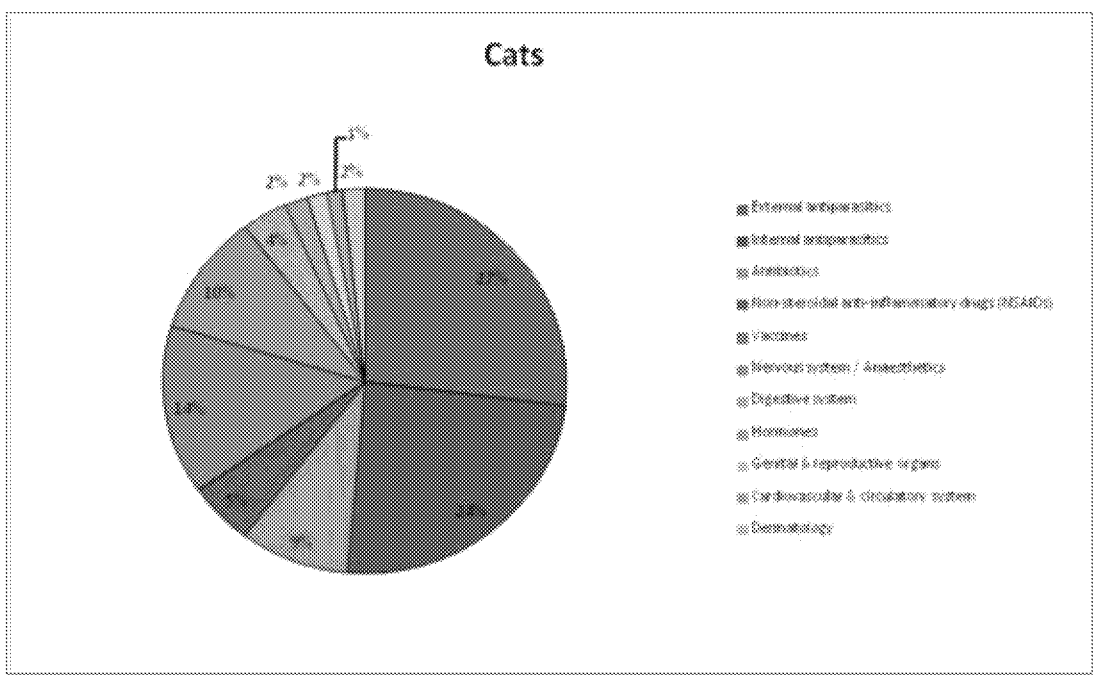
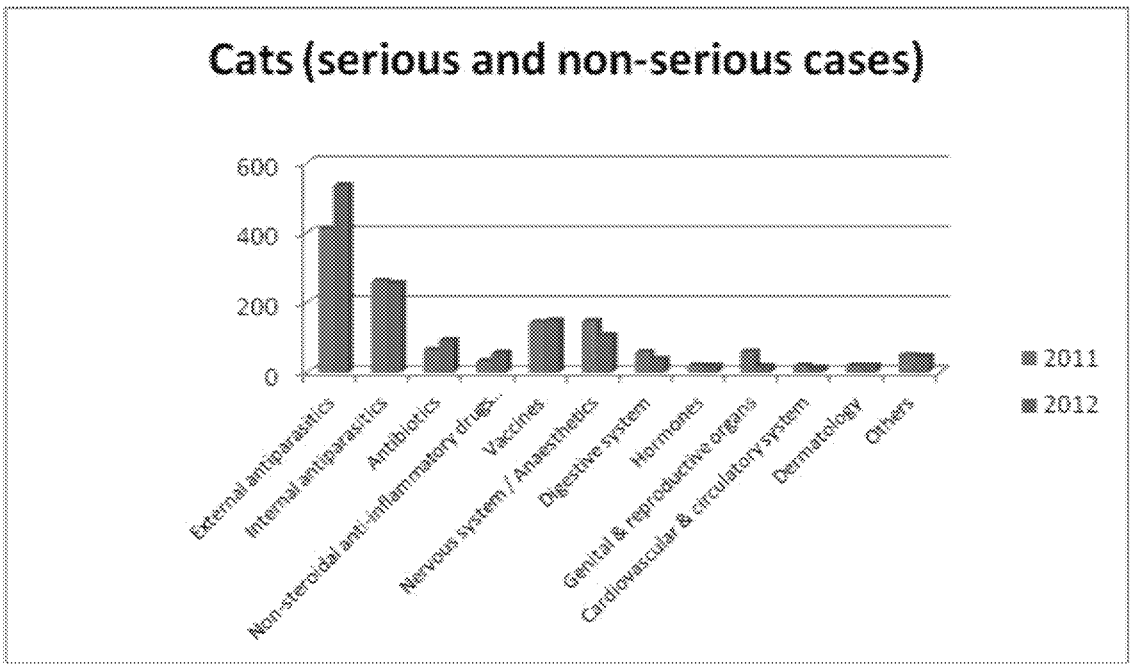


Not including reports related to the use of permethrin in cats, adverse events by therapeutic category were broken down as follows:



The proportion relating to external antiparasitics then becomes 27% (against 41% with permethrin) and in terms of breakdown, non-serious cases then account for 83% of reports collected for this therapeutic category.

Compared to 2011, there was mainly a sharp increase in reports concerning external antiparasitics (33% in 2011 against 41% in 2012) and a decrease in cases related to agents acting on the nervous system – primarily anaesthetics (15% in 2011 against 8% in 2012).



However, these figures need to be qualified because of the investigation conducted in 2012 on the adverse events related to SERESTO collars, for which the MA holder submitted a series of non-serious cases, 86 of which were adverse reactions (most often localised skin reactions) in cats.

To be able to compare these results with those of 2011, these 86 cases should be excluded. The proportion of cases related to external antiparasitics (excluding permethrin) in cats then becomes 20% in 2012 against 16% in 2011.

Concerning the clinical profile of the reported adverse events, it is quite consistent with the general trend described in the previous paragraphs. However, all cases combined, the symptomatology of the cases involving external antiparasitics proves significantly more serious because of the many cases involving permethrin (whose typical toxic effects in cats primarily include severe tremors and convulsions, which can lead to the death of the animal). Leaving aside these specific cases, the profile of the cases associated with other antiparasitics appears very similar to that described in dogs, essentially neurological signs (lethargy, ataxia, mild tremors) and gastrointestinal disorders in the event of ingestion (vomiting, anorexia, diarrhoea).

Likewise, still in the category of external antiparasitics, local reactions at the application site (depilation, itching, erythema, and occasionally ulcers, whether or not associated with a bacterial infection) are noticeably overrepresented because of the additional cases submitted as part of the investigation into SERESTO collars.

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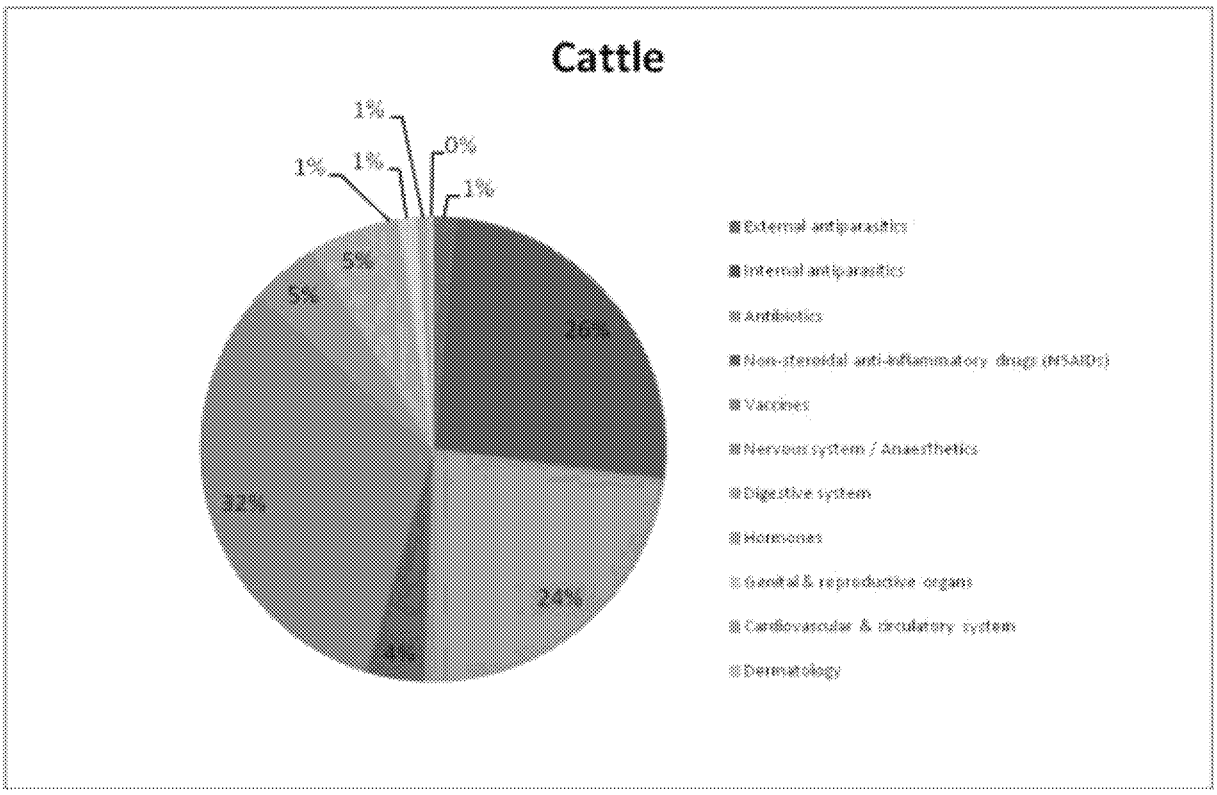
Apart from the special circumstances mentioned above, the clinical profile of the other cases is fairly classic, depending on the therapeutic categories concerned: nervous and gastrointestinal signs for antiparasitics (as well as local reactions at the application site for external formulations), and febrile and anaphylactic reactions (and inflammatory reactions at the injection site), essentially for vaccines.

III.3.c - Cattle

For cattle, vaccines alone accounted for 32% of all reports, followed by internal antiparasitics in 26% of reports and antimicrobials in 24%.



Within the antimicrobials category, approximately 47% of the products involved were beta-lactams (including 5% cephalosporins), which are also the most widely used antimicrobials in cattle (see the ANSES report "Sales survey of veterinary medicinal products containing antimicrobials in France in 2012"). Macrolides followed, with 17% of antimicrobials involved, while quinolones accounted for just over 6%.

In cattle, the reports relate mainly to serious cases (84%). However, given the requirements of livestock production systems, the problems (especially adverse events) likely to be encountered with veterinary drugs are only generally reported – to veterinarians and therefore to the competent authorities – when the zootechnical and/or financial consequences are significant. Thus, reports mainly concern only serious cases.

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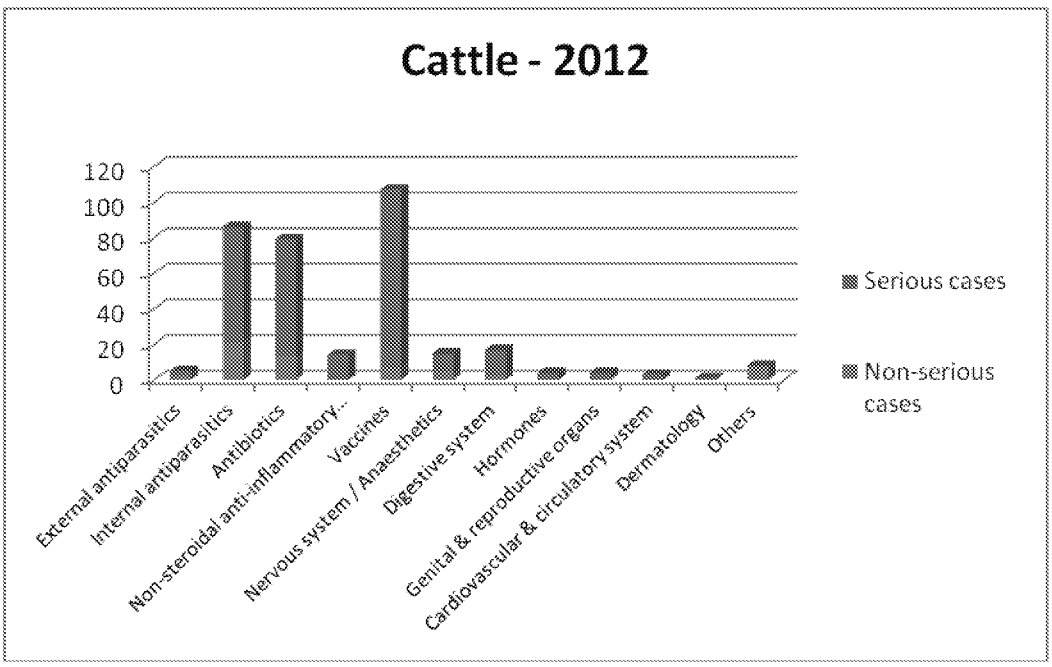

Due to the reporting of mainly serious cases in cattle – compared to domestic carnivores – and the significantly different profile of the products used (with a very high preponderance of internal antiparasitics on external formulations), the clinical profile of the adverse events reported also varies. Indeed, while the nature of the clinical signs associated with the different therapeutic categories is consistent with the general trend, their relative weight is modified. Therefore, since vaccines are the most frequently cited products, the main symptoms described concern anaphylactic reactions (and more rarely febrile events). Moreover, these hypersensitivity reactions are not specific and may also occur with other products such as antimicrobials (also mentioned more here than in dogs and cats).

Cases of reproductive disorders (including abortions) are also proportionally more frequent than in pets, whether they relate to (suspected) direct effects of products or the consequences of other mechanisms (especially severe fever or hypersensitivity reactions).

Lastly, because of the specific nature of livestock production in terms of epidemiological context, treatment methods and performance monitoring, the respective share of suspected cases of lack of efficacy is much higher in cattle, compared to other species (particularly domestic species). These cases are analysed in the next chapter.

Compared to 2011, a decrease was noted in reports involving vaccines (43% in 2011 against 32% in 2012). This decrease is probably related to the drop in cases related to vaccines against bluetongue. Indeed, in 2011, with 60 reports, bluetongue cases accounted for 42.6% of all reports involving vaccines, while in 2012, only 24 reports concerned vaccines against bluetongue, or 22% of all cases observed for this therapeutic category.

There was also an increase in reports related to internal antiparasitics (12% in 2011 against 26% in 2012).

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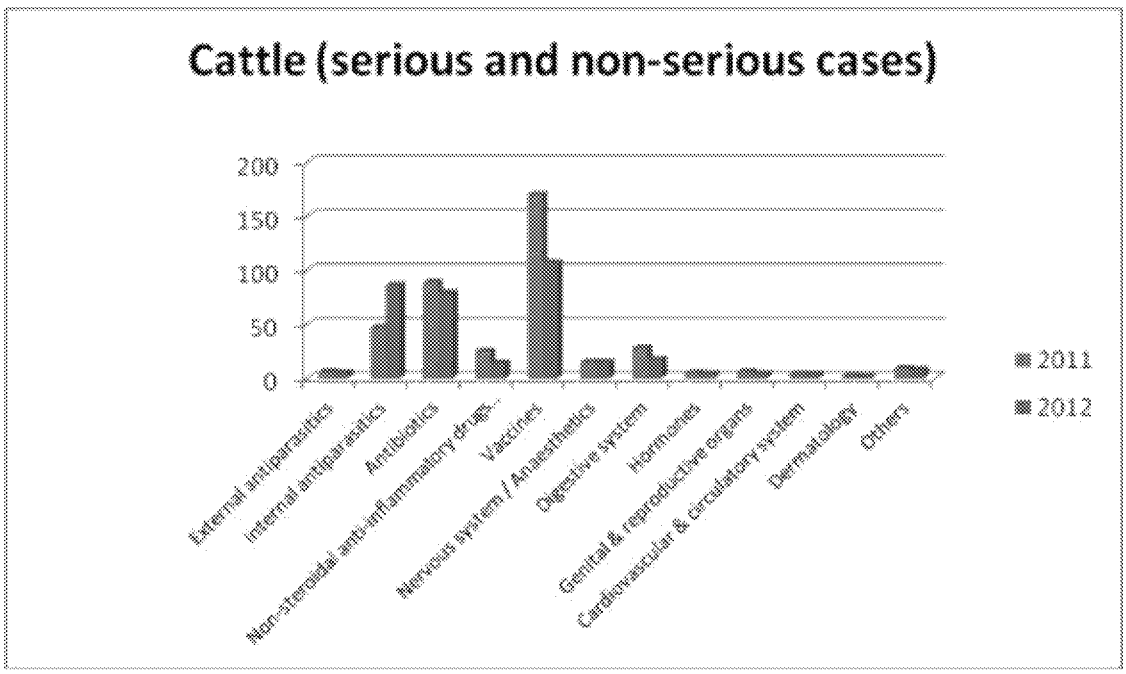

III – 4 BREAKDOWN OF CASES BY TYPE OF INFORMATION

Adverse events typically reported include adverse reactions to veterinary medicinal products in the strict sense, suspicions of lack of efficacy, information on potential environmental risks and information on the validity of withdrawal periods for veterinary medicinal products. The following table shows how the cases reported in 2012 were broken down into these various categories.

Adverse reactions in animals	2872
Lack of efficacy	177
Residue issues	9
Environmental issues	0

As in previous years, cases of adverse reactions in animals made up a clear majority (94%).

Suspicions of lack of efficacy accounted for 5.8% of all reports and other cases accounted for less than 1%. However, since these reports generally related to non-serious cases, they were submitted to the ANMV by MA holders in PSURs and not immediately as the cases occurred.

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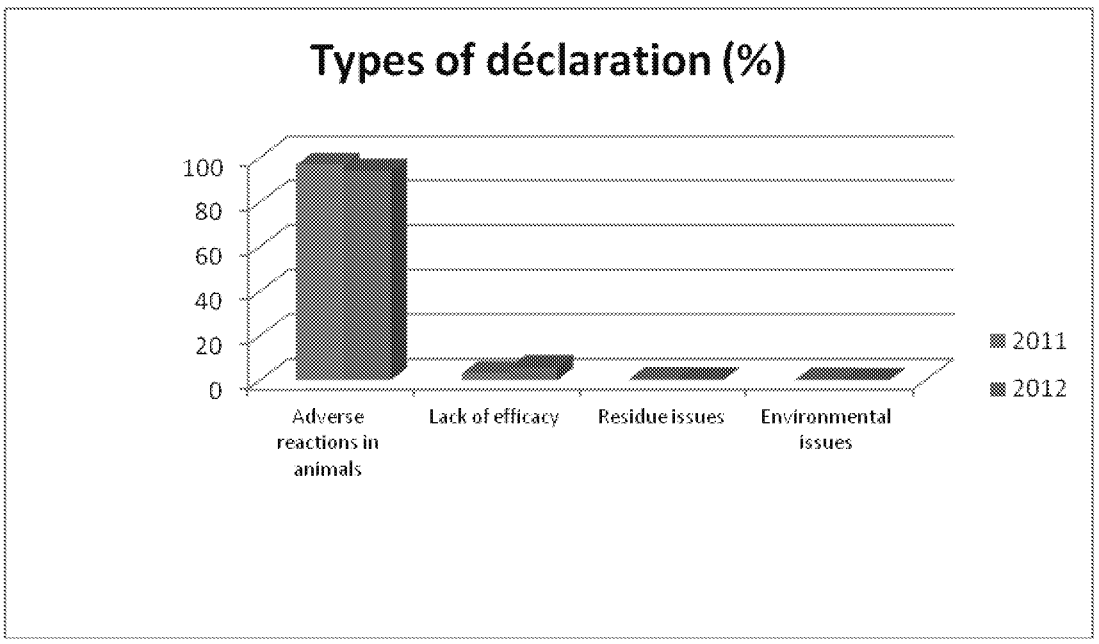
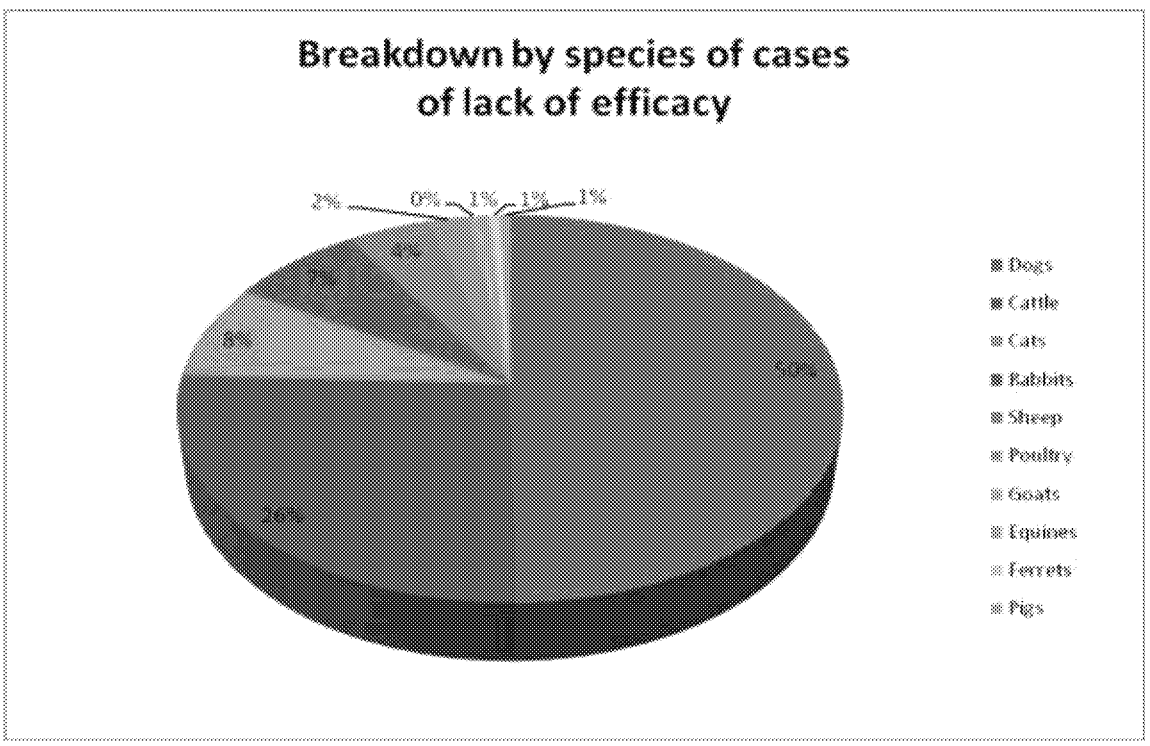


Suspicions of lack of efficacy

Compared to 2011, with 177 reports against 89, there were nearly twice as many reports of lack of efficacy in 2012.



The species most represented in reports concerning lack of efficacy were, as in 2011, dogs (50%) and cattle (26%).

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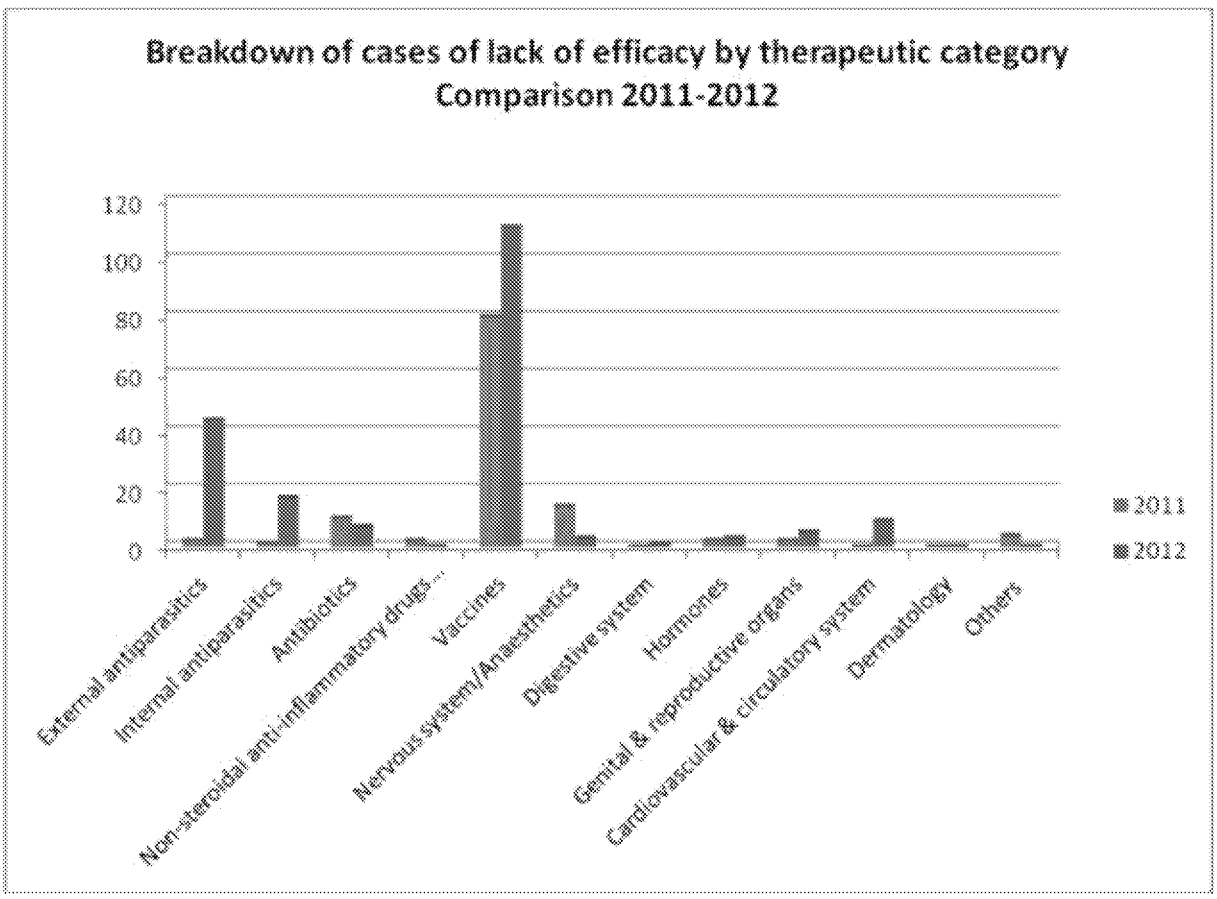
Moreover, the vast majority of cases of lack of efficacy reported in 2012 were serious (116 serious cases out of 177 reports of lack of efficacy).

Like the previous year, cattle formed a large share in this sub-category compared to the total number of cases by species (where cattle accounted for less than 10% of the total).

Compared to last year, the relative share of dogs grew from 38% in 2011 to 50% in 2012. However, the 2012 figures are supplemented in particular by the investigation conducted in 2012 on the adverse events from SERESTO collars, for which the MA holder submitted 36 cases of suspected lack of efficacy in dogs.
However, compared to 2011, there was also an increase in reports of lack of efficacy for different therapeutic categories, especially external antiparasitics, but also internal antiparasitics and vaccines.



The vast majority of cases of lack of efficacy related to vaccines, with 73% in dogs, 67% in cats and 60% in cattle. Very often, the suspected lack of efficacy was based on the occurrence of disease in the vaccinated animals, yet some products are only intended to provide partial protection against certain symptoms.

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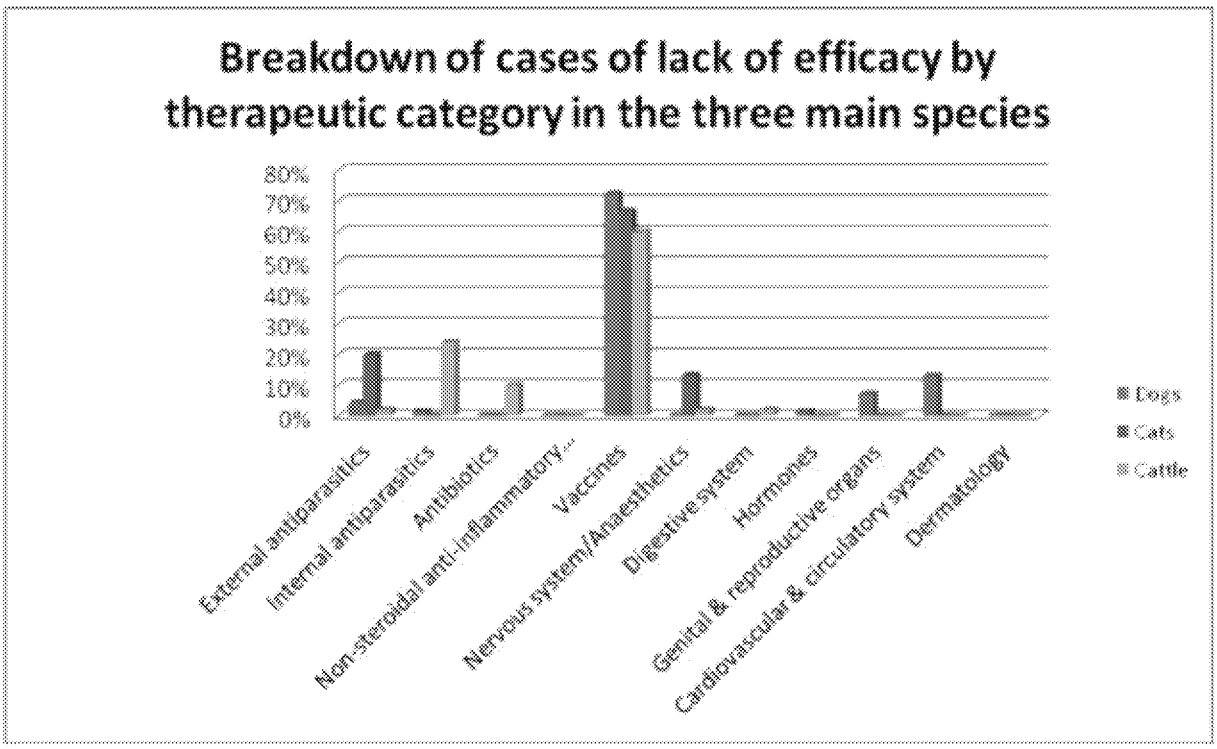
Moreover, the vaccine protocols (number of injections to perform, precise timetable, minimum age of animals, etc.) necessary to achieve effective immunity may not always be followed (in particular when the disease occurs before the end of primary vaccination). Assessing these cases is quite complex and requires consideration of multiple factors, and most of the time the vaccines' conditions of use (failure to follow protocols, pre-existing infections at vaccination, etc.) mean that no conclusions can be drawn about a possible failure in the products.



Besides vaccines, the other categories of veterinary drugs mainly involved in a suspected lack of efficacy were antiparasitics: external in domestic carnivores (respectively 20% of cases of lack of efficacy reported in cats and 4% in dogs, excluding cases from the SERESTO investigation) and internal in cattle (24%). However, as with vaccines, it is generally difficult to reach any conclusion about a possible lack of efficacy of the drug used, because several other factors, including infestation pressure in the animal environment, are also involved.

In addition, in cattle in particular, antimicrobials are also regularly involved in suspicions of lack of efficacy. However, like vaccines or antiparasitics, the characteristics of the epidemiological context and the overwhelmingly multifactorial nature of animal diseases encountered in livestock rearing often make it difficult to accurately assess the efficacy of these drugs. Thus, a given compound may for example be effective against a particular bacterium (in accordance with its indications), but not enough to completely cure a disease that involves other factors as well (other bacteria that are not susceptible to the product, viral coinfection, emergence of resistance, environmental factors, etc.).

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In domestic carnivores, the other therapeutic categories involved in the suspicions of lack of efficacy were:

- anaesthetics and sedatives (especially regarding unsatisfactory results of anaesthetic protocols)
- drugs with cardiac or circulatory action, used mainly in the treatment of long-term conditions such as heart or kidney failure, for which the therapy, although effective, can often only delay the progression of symptoms).

Issues of residues

Like last year, cases involving suspicions of veterinary drug residues in milk were reported. The nine reports that were submitted to the ANMV in 2012 all involved milk samples declared 'positive' for inhibitors under the official method for testing for antimicrobial residues in milk, although the compound(s) responsible were neither quantified nor identified.

Since the beginning of 2011, in the framework of milk quality monitoring, the French dairy industry association has been using a new screening test: ECLIPSE 3G. The switch to this test was primarily driven by a need to improve the detection of tetracyclines, which in 2010 were the most commonly used category of antimicrobials in dairy cattle in France (see "Sales Survey of Veterinary Medicinal Products Containing Antimicrobials in France - 2010", available on the ANSES website).

Depending on test sensitivity, some compounds can be detected below the MRL (Maximum Residue Limit), others above it and the majority around it.

To use these positive results to call into question drug withdrawal periods, it is necessary to ensure that the inhibitor detected is indeed the suspected compound and that the drugs involved have been used in accordance with their SPCs, then to undertake a specific quantitative analysis of residues in the affected milk samples and find a residue level above the MRL after the withdrawal period has elapsed. Based on the data submitted in the reports, it is not presently possible to draw any conclusions regarding the presence of veterinary drug residues, due to the use of qualitative multiresidue testing that is unable to define the levels or nature of the residues found in the samples. Therefore, all of these reports have been classified in category 'O'. It should be noted however that this type of report is important: even though their individual case assessments do not appear satisfactory, they can serve as alerts to the appearance of new potential problems.

As a result of the mobilisation of the various stakeholders affected by this issue, a draft protocol should soon be finalised for the qualitative and quantitative analysis of positive samples.

It should also be noted that, independently of pharmacovigilance, the public authorities implement a plan for the monitoring and control of veterinary drug residues in the food chain every year so as to ensure compliance with the regulatory limits.

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Environmental problems

No environmental problems were reported in 2012.

Off-label use

The French Public Health Code (Article L.5143-4) defines the conditions under which a veterinary practitioner can prescribe the use of a medicinal product outside the scope of its authorisation. Of the 3058 animal cases reported in 2012, 1028 (approximately 34% of reports) involved uses outside the terms defined in the marketing authorisations. However, this number is probably underestimated, since apart from obvious cases, such as a target species not provided for in the MA, and in the absence of a formal mention of off-label use, adverse events are by default considered to have occurred following administration within the framework of a medicinal product's authorisation.

The main species involved were cats (54% of reports), dogs (30%) and cattle (5%). This breakdown by species is fully comparable to the results obtained in 2011, with respectively 52%, 32% and 6% in these three species.

It may also be noted that 6.3% of off-label reports related to Exotic pets/Wildlife, despite them accounting for only 1% of total reports in animals in 2012. This result is not surprising since few veterinary drugs are authorised in these minority species. These reports related mainly to pet rabbits and ferrets.

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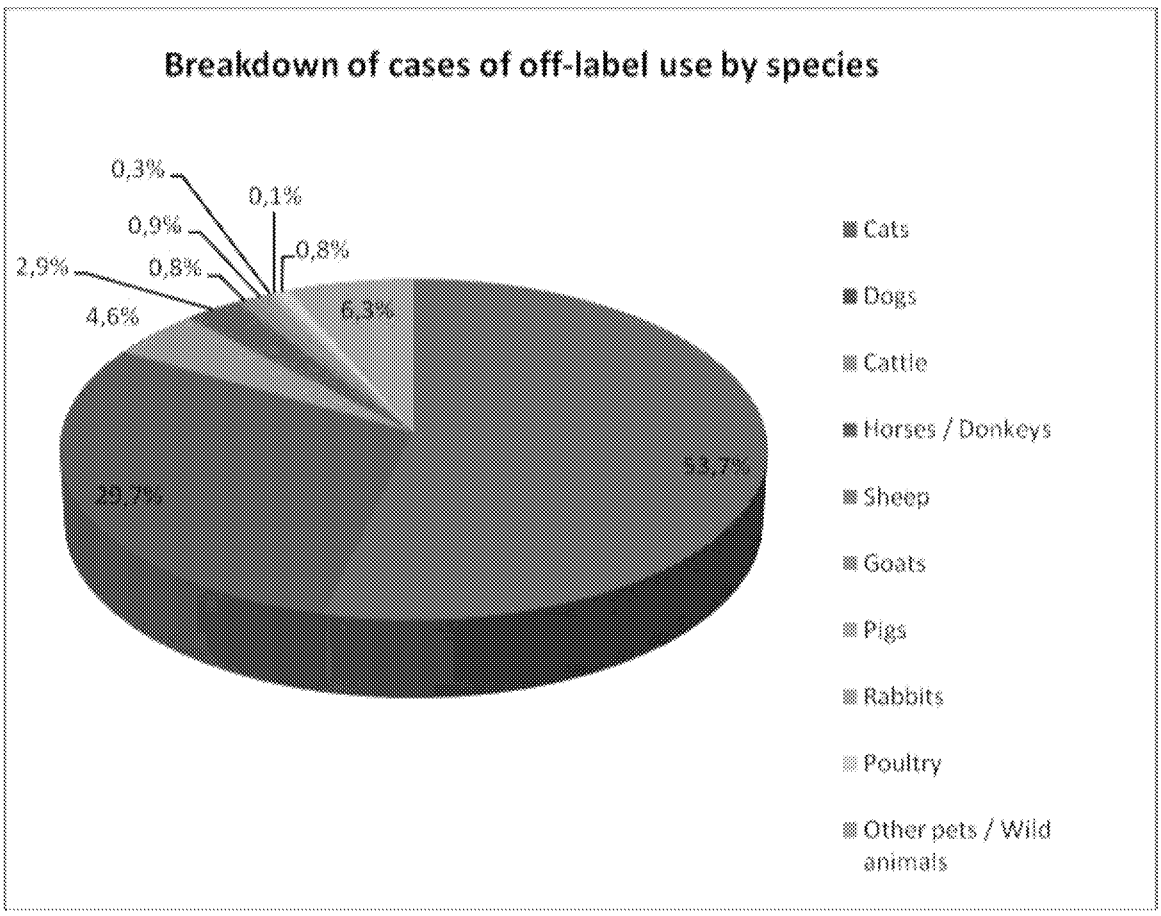

The marked predominance of feline species in these figures is partly due to the many cases (244) reported following off-label use in cats of permethrin-based antiparasitics intended for dogs. If these data are excluded, the relative share of dogs and cats in the effects reported following off-label use of veterinary drugs is almost identical, at 39% for each of these species.
However, even setting aside the permethrin cases, antiparasitics are still implicated in the vast majority (about two thirds) of off-label uses reported in cats: they mainly concern overdoses, use in cats of products intended for dogs and/or administration errors (ingestion of products intended for dermal application).

These trends are also seen in dogs, where again antiparasitics alone account for more than half of the reported cases of off-label uses, with very similar descriptions: mainly dosing errors, the use in dogs of products intended for other species (usually cattle or horses) and the ingestion (accidental by the animal or following an administration error) of drugs for external use.

In cattle, the respective shares of the different therapeutic categories were more balanced, and none stands out as clearly as for domestic carnivores. Overall, reports involving off-label use essentially concerned dosing errors and non-compliance with the products' therapeutic indications and/or routes of administration.

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IV - THE MOST COMMONLY MENTIONED MEDICINAL PRODUCTS IN SERIOUS ADVERSE EVENT REPORTS IN 2012

The following table (see page 44) summarises the 35 veterinary drugs that were mentioned in at least **ten serious cases** in 2012.
To count serious cases, a search by range name was undertaken and then those drugs that differ from one another by dosage (or concentration) only were grouped together.
Thus, several drugs correspond to the names of the ranges listed below:

- Advantix Spot-On: 4 types of pipettes (Advantix Very Small Dogs, Advantix Small Dogs, Advantix Medium Dogs and Advantix Large Dogs);
- Atopica: 3 types of capsules (25 mg, 50 mg and 100 mg);
- Certifect: 4 types of pipettes (Certifect for Dogs 2-10 kg, Certifect for Dogs 10-20 kg, Certifect for Dogs 20-40 kg and Certifect for Dogs 40-60 kg);
- Comfortis: 5 types of chewable tablets (270 mg, 425 mg, 665 mg, 1040 mg and 1620 mg);
- Milbemax tablets: 2 types of tablets (Milbemax film-coated tablets for small cats and kittens and Milbemax film-coated tablets for cats);
- Previcox tablets: 2 types of chewable tablets (57 mg and 227 mg);
- Profender tablets: 3 types of tablets (Profender Tablets for Small Dogs, Profender Tablets for Medium Dogs and Profender Tablets for Large Dogs);
- Profender Spot-On: 3 types of pipettes (Profender Spot-On Solution for Small Cats, Profender Spot-On Solution for Medium Cats and Profender Spot-On Solution for Large Cats);
- Stronghold: 6 types of pipettes (15 mg, 30 mg, 45 mg, 60 mg, 120 mg and 240 mg);
- Trocoxil: 5 types of chewable tablets (6 mg, 20 mg, 30 mg, 75 mg and 95 mg);
- Zoletil: 3 doses of injectable solution (20, 50 and 100).

Of these 35 veterinary drugs identified, 27 concern only pets in the authorised target species, 5 concern only production animals and three are intended for both of the preceding categories.
In terms of therapeutic category, 16 of the reported drugs were vaccines, 10 were antiparasitics (internal or external) and three were non-steroidal anti-inflammatory drugs (NSAIDs).

The risks related to the use of these veterinary medicinal products were assessed based on this classification. These risks were estimated for whole populations through:

- Quantitative criteria: calculation of the incidence of adverse events, i.e. for a given period, the ratio of the number of animals having these adverse events to the number of treated animals;
- Qualitative criteria: study of the clinical profiles of the observed events.
-

$$Incidence = \frac{\text{Number of animals reacting after administration of the drug *}}{\text{Number of animals treated during the period}}$$

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*: Number of animals reacting for which the causality of the "drug" is A, B, O or O1. Cases in which it was shown that the administered medicinal product was not responsible for the adverse event are not taken into account in this calculation (which therefore excludes reports for which the assessed medicinal product was categorised as N).

The number of animals treated is calculated from the sales volume of the medicinal product. For an "isolated" medicinal product authorised for a single species, the calculation of the number of animals treated is relatively easy.

When reports highlighted adverse events occurring in non-authorised species, sales volumes for these species could not be estimated. Total sales were linked to authorised target species and could not therefore be used to estimate the frequency of adverse events in non-authorised species. Incidence is therefore not an appropriate parameter for assessing risk in non-authorised species. In this particular case, the assessment took into account the severity of clinical signs, the number of reports and its progression over time.

It should nevertheless be kept in mind that incidence is relative. Indeed, the calculation methods used are based, at a given time, on the number of reported cases (not the number of actual cases, which is unknown) and the estimated number of treated animals. How easy it is to quantify this number will depend on the drug in question. Between a drug authorised for a single species as a single dose and another authorised for several species and/or with dosing related to the animal's weight and/or with several authorised dosing schedules, the degree to which the estimated number of treated animals reflects reality will vary. In this section, for medicinal products authorised for several target species, incidence has first been calculated by species. Since these specific incidence rates do not show any significant phenomena for pairs of products and target species, the table shows cumulative incidence rates, all target species combined.

The frequency categories for adverse events are defined as follows, based on the calculated incidence values:

- **Very common** if more than one treated animal in 10 is likely to react
- **Common** if 1-10 treated animals in 100 are likely to react
- **Uncommon** if 1-10 treated animals in 1000 are likely to react
- **Rare** if 1-10 treated animals in 10,000 are likely to react
- **Very rare** if less than one treated animal in 10,000 is likely to react

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Alphabetical list of veterinary medicinal products mentioned in at least ten serious cases in 2012

Product	Target species	Route of administration	Therapeutic category	Frequency of serious cases
Advantix Spot-On	Dogs	Dermal	Ectoparasiticide	Very rare
Atopica	Dogs	Oral	Selective immune suppressant	Very rare
Bovilis bovigrip	Cattle	Injectable	Vaccine	Rare
BTVPur Alsap 1-8	Cattle, Sheep	Injectable	Vaccine	Very rare
Canigen DHPPI/L	Dogs	Injectable	Vaccine	Very rare
Canileish	Dogs	Injectable	Vaccine	Rare
Carbesia	Cattle, Dogs	Injectable	Internal antiprotozoal	Very rare
Certifect	Dogs	Dermal	Ectoparasiticide	Very rare
Closamectin Pour-On for cattle	Cattle	Dermal	Endectocide	Very rare
Comfortis	Dogs, Cats	Oral	Ectoparasiticide	Rare
Convenia	Dogs, Cats	Injectable	Antimicrobial agent	Very rare
Enduracell 7	Dogs	Injectable	Vaccine	Very rare
Eurican CHPPI2	Dogs	Injectable	Vaccine	Very rare
Eurican CHPPI2-L	Dogs	Injectable	Vaccine	Very rare
Eurican CHPPI2-LR	Dogs	Injectable	Vaccine	Very rare
Frontline Combo Spot-On for cats	Cats	Dermal	Ectoparasiticide	Very rare
Imalgene 1000	Dogs, Cats, Cattle, Sheep, Goats, Horses, Pigs, laboratory animals, wild animals, birds	Injectable	Anaesthetic/ sedative	Rare
Imaveral	Cats, Dogs, Cattle, Horses	Dermal	Antifungal	Rare
Leukocell 2	Cats	Injectable	Vaccine	Very rare
Metacam 5 mg/ml injectable solution for dogs and cats	Dogs, Cats	Injectable	NSAID	Very rare
Milbemax tablets	Cats	Oral	Endoparasiticide	Very rare
Nobivac Lepto	Dogs	Injectable	Vaccine	Rare
Nobivac CHPPI	Dogs	Injectable	Vaccine	Very rare
Nobivac Myxo-RHD	Rabbits	Injectable	Vaccine	Rare
Previcox tablets	Dogs	Oral	NSAID	Very rare
Profender tablets	Dogs	Oral	Endoparasiticide	Very rare
Profender Spot-On	Cats	Dermal	Endoparasiticide	Very rare

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Product	Target species	Route of administration	Therapeutic category	Frequency of serious cases
Purevax RCP FELV	Cats	Injectable	Vaccine	Very rare
Purevax RCPCH FELV	Cats	Injectable	Vaccine	Very rare
Stop M	Cattle	Injectable	Antimicrobial agent	Very rare
Stronghold	Dogs, Cats	Dermal	Endectocide	Very rare
Trocoxil	Dogs	Oral	NSAID	Uncommon
Vanguard 7	Dogs	Injectable	Vaccine	Very rare
Versifel CVR	Cats	Injectable	Vaccine	Very rare
Zoletil	Dogs, Cats	Injectable	Anaesthetic/ sedative	Very rare

Note: The vaccine Pregsure BVD® should also appear in this table, as it was mentioned in more than ten serious cases in 2012. However, since the reported events (bovine neonatal pancytopaenia in calves born to mothers vaccinated in previous months/years) appeared very late after administration and because the product was withdrawn from the market in summer 2010, no calculation of incidence could be undertaken for 2012.

Of the 35 veterinary drugs appearing in this classification, 10 had already been mentioned in 2011: Advantix Spot-On, BTVPur Alsap 1-8, Enduracell 7, Eurican CHPPI2, Eurican CHPPI2-L, Eurican CHPPI2-L-R, Frontline Combo Spot-On for cats, Previcox tablets, Purevax RCP FELV, Trocoxil and Zoletil. For these drugs, the frequency of adverse events recorded remained the same, except for Enduracell 7, which went from rare to very rare.
Regarding ADVANTIX SPOT-ON, as in 2011, the vast majority of serious adverse events reported involved cats (96.5% of animals affected in 2012), despite this drug being contraindicated in this species.
At the same time, it should be noted that in 2012, 25 new drugs were involved in ten or more reports of serious cases. However, it should be borne in mind that the number of reports is not a sufficient criterion for estimating the potential risk associated with the use of a drug, and account must also be taken of the number of animals treated, the effects mentioned in the SPC and the change in data over time.

Of the 35 products mentioned in at least ten serious cases in 2012, none had an incidence rate of more than one case per 100 treated animals. The vast majority even had an incidence of less than one case per 10,000 (very rare frequency).

In 2012, eight drugs had an incidence of more than one case per 10,000: TROCOXIL®, CANILEISH®, COMFORTIS® and NOBIVAC MYXO-RHD®, which all have a centralised MA; and BOVILIS BOVIGRIP®, IMALGENE 1000®, IMAVERAL® and NOBIVAC LEPTO® which have a purely national MA. It should be noted that only TROCOXIL® also had an incidence of this magnitude in 2011.

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For these eight medicinal products, a review of the situation is presented below.

TROCOXIL®, a non-steroidal anti-inflammatory drug, is a range of five types of chewable tablets (6, 20, 30, 75 and 95 mg) intended exclusively for dogs. The active substance is mavacoxib of the coxib class. Coxibs act by inhibition of COX-2 (cyclooxygenase), which stimulates the synthesis of prostaglandins as mediators of inflammation.
Because of their mode of action, non-steroidal anti-inflammatory drugs may potentially interfere with the mechanisms of protection of the gastrointestinal mucosa, thereby increasing the risk of developing gastric and/or duodenal ulcers. They can also modify blood flow to the glomeruli, thereby causing acute kidney failure. These effects are not specific to Trocoxil; nevertheless they are well known and have been documented in the summary of product characteristics and the package leaflet.
The vast majority of cases reported in 2012 described these kinds of symptoms.

CANILEISH® is a vaccine against canine leishmaniasis. Following the reports submitted, further information was added to this drug's SPC in 2012 (see Section V – 4).
The vast majority of cases recorded by ANSES-ANMV in 2012 following the use of this vaccine reported hypersensitivity reactions such as allergic oedema and/or anaphylactic shock (which can be fatal). However, these effects are related to the specific sensitivity of certain animals, and, even if they are mentioned in the SPC, they are absolutely not specific to Canileish. In fact, similar cases are regularly reported with virtually all types of drugs (especially vaccines).

COMFORTIS® is an oral antiparasitic against fleas in dogs and cats, and comprises a range of five chewable tablets (270 mg, 425 mg, 665 mg, 1040 mg and 1620 mg). The active ingredient is spinosad. The effects reported in 2012 mainly concerned dogs, with a symptomatic profile fairly consistent with the SPC indications: lethargy, ataxia, anorexia, vomiting, etc. However, several cases reporting more unexpected symptoms (including ophthalmologic disorders) were also identified and are being investigated at European level.

NOBIVAC MYXO-RHD is a live vaccine for myxomatosis and rabbit haemorrhagic disease.
The adverse events related to this vaccine were mainly divided into two categories: suspected post-vaccination reactions and suspected lack of efficacy.
The number of cases reported should be interpreted with caution because this vaccine only recently came on the market (the pharmacovigilance data is therefore too recent). These data are currently being assessed by experts at European level.

BOVILIS BOVIGRIP is an inactivated vaccine against respiratory diseases in cattle caused by bovine respiratory syncytial virus parainfluenza-3 viruses and *Mannheimia haemolytica.*
As with the NOBIVAC MYXO-RHD above, the reported adverse events associated with this vaccine are mainly of two types:

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- Post-vaccinal hypersensitivity reactions, generally causing severe respiratory disorders that can be fatal. Although not specifically mentioned in the SPC, these effects are quite well known with vaccines;
- Suspected lack of efficacy. However, given the multifactorial aetiology of respiratory diseases in cattle (and the sometimes insufficient information about the vaccine protocols), it is often difficult to confirm a real lack of vaccine protection.

IMALGENE 1000 is an injectable general anaesthetic containing ketamine, authorised in multiple species (dogs, cats, cattle, sheep, goats, horses, pigs, laboratory animals, wild animals and birds).
Because of its mode of action, this drug may induce significant cardio-respiratory depression. This can also be aggravated by the (frequent) use of combined protocols involving other compounds (xylazine, medetomidine, etc.). The risk of resulting anaesthetic complications is well known (and mentioned in the SPC) and justifies the special monitoring implemented during anaesthesia. However, the occurrence of anaesthetic accidents remains inevitable, even though their frequency is limited.

IMAVERAL is an external antifungal, whose active substance is enilconazole. It is authorised for the treatment of ringworm in cats, dogs, cattle and horses.
The symptoms in the adverse events reported in 2012 for this product are fairly consistent with the SPC indications: mainly gastrointestinal (hypersalivation, vomiting, anorexia) and nervous symptoms (lethargy, ataxia, convulsions). A few cases involved mortality, especially when the drug was used in non-target species (turkeys, rabbits).

NOBIVAC LEPTO is an inactivated vaccine against leptospirosis in dogs caused by *Leptospira interrogans* serogroups Canicola and Icterohaemorrhagiae.
As with the vast majority of vaccines, the main adverse events reported were post-vaccination hypersensitivity reactions (allergic oedema, anaphylaxis) and local reactions at the injection site (in accordance with the indications of the SPC). Some cases of suspected lack of efficacy were also recorded, but they are often difficult to interpret, especially given the variety of strains of *Leptospira* (the vaccine only effectively protects against two specific serogroups of *Leptospira interrogans*).

Concerning drugs for which incidence in 2011 was greater than 1 case per 1000, but which do not appear in the 2012 rankings, a description of how they were monitored is given below:

PORCILIS AR-T DF® is a vaccine given to sows for the prevention of progressive atrophic rhinitis in piglets. In 2010, the vector used to express Protein dO of the dermonecrotic toxin was modified. Following this change, an increase in the number of reports of adverse events involving abortions and anaphylactic reactions was observed in 2011, mainly in France. Following an expert appraisal of these data at European level, the CVMP recommended adding in the "Adverse reactions" section of the SPC the sentence: *"In very rare cases, anaphylactic reactions and abortions have been reported."*
However, as of 1 July 2013, the corresponding application to amend the SPC had not been submitted.

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IMPROVAC® is a vaccine used as an alternative to physical castration of boars. In 2011, an increase in the incidence of adverse events, relating to anaphylactic reactions, was observed in France but not in other EU Member States. Moreover, in some reported cases, the reaction was not observed after the first injection.

This type of reaction is already described on the SPC for IMPROVAC®, but with a "very rare" frequency, and the clarification that animals generally react on the first injection but not subsequently. A European expert appraisal of the pharmacovigilance data in 2012 did not confirm this development: the incidence of anaphylactic reactions has again become very rare throughout Europe, and the vast majority occur after the first injection only. The CVMP did not therefore recommend modifying the SPC, which still states:

"In very rare cases anaphylactoid type reactions (dyspnoea, collapse, cyanosis and hypersalivation associated with or without muscle twitching or emesis) have been observed within a few minutes after the first vaccination with duration up to 30 minutes. In a small number of animals death occurred following the reaction, however most animals recovered without treatment and did not appear to react to subsequent vaccinations."

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V – KEY EVENTS IN 2012

V – 1 Exemption from regulation of poisonous substances intended for veterinary medicine

The French Public Health Code, and in particular Articles L.5132-1 and R. 5132-2, provides for the classification by Ministerial Order of certain substances and preparations used in the composition of drugs, such as poisonous substances, and if necessary, the possibility of exemption under certain conditions from the requirements ensuing from this classification. If a Ministerial Order for registration or exemption concerns a veterinary medicinal product, the Director General of the French National Agency for Medicines and Health Products Safety seeks the opinion of ANSES before proposing it for signature by the competent ministers.

On 16 January 2012, ANSES received a formal request from the French National Agency for Medicines and Health Products Safety (ANSM) for an opinion on a draft Ministerial Order on exemption from regulation of certain poisonous substances used in the composition of veterinary drugs.

The active substances contained in veterinary medicinal products are, with rare exceptions, classified as poisonous substances on the basis of classifications introduced when the drug is used in humans. There are, however, specific provisions for exemption under a Ministerial Order of 20 July 1949 amended by a Ministerial Order of 3 December 1986.

The Ministries of Agriculture and Health decided to revise the existing provisions and the lists of substances or preparations concerned, due to the obsolete nature, therapeutically speaking, of the exempt substances and the benefit of hindsight regarding pharmacovigilance on certain drugs.

A working group was set up by the ministries to review the conditions of use of the exempt veterinary drugs, mainly intended for pets, and the proposals. This working group consisted of representatives of veterinary medicine professionals (orders of pharmacists and veterinarians, unions representing private veterinarians and dispensing pharmacists, the SIMV), the ANSM, and the French Agency for Veterinary Medicinal Products (ANMV). After consultation, a list of drugs eligible for the exemption rules was proposed to the ANMV for evaluation.

In this context, the ANMV was asked to conduct, in conjunction with the CNMV, a scientific assessment of the existing exemptions and those requested by health professionals.

The following assessment criteria were selected:

- therapeutic indications, dosage and duration of treatment;
- contents of the SPC, when one exists, especially the "contraindications" and "adverse reactions" sections;
- **pharmacovigilance data**;
- whether or not a preliminary veterinary examination is necessary;
- size of the presentations (number of tablets, volume, etc.) in conjunction with the dosages and durations of treatment.

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The results of this work were sent to ANSM for the drafting of the Ministerial Order that was the subject of the formal request.

This exercise led to the publication of the Ministerial Order of 24 April 2012 on the exemption from regulation of poisonous substances intended for veterinary medicine, which repealed the Ministerial Order of 20 July 1949 as amended by the Ministerial Order of 3 December 1986.

The lists of exempt substances have been drastically reduced compared to previous lists. A number of initially exempt active substances are no longer exempt, or the conditions for their exemption have been modified. Other poisonous substances have become exempt for the first time. Psychotropic drugs or narcotics, corticosteroids, antimicrobials, local anaesthetics, NSAIDs (non-steroidal anti-inflammatory drugs) and products for the prevention of oestrus have been removed because of the risks of misuse or the pharmacovigilance cases encountered. The drugs that have been kept are essentially antiparasitics in oral form, to which have been added new substances belonging to this therapeutic category.

The doses adopted are consistent with the unitary dosages used and validated by the MA. The amounts provided to the public are consistent with an occasional treatment adapted to the indications.

The list of drugs affected by these changes in dispensing conditions is available on the ANSES website (www.Anses.fr).

V – 2 Intramammary "dry cow" products

During 2011, reports of cases of mortality in cows following peracute mastitis that occurred at dry-off after administration of intramammary "dry cow" ointments were received by the ANMV. These reports were difficult to interpret in terms of involvement of the drug itself, treatment (medical procedure), and the cow's environment (hygiene conditions, distance from the milking environment). Indeed, according to one of the MA holders concerned, the bacterium causing the peracute mastitis *(Pseudomonas aeruginosa* in general) was already present in the udder before treatment, and when milking ceased this resulted in the accumulation of toxins in the udder. The mortality observed was therefore unrelated to the drug or treatment. However, the French Commission for Veterinary Medicinal Products concluded in its 2005 report that colonisation of the udder took place during or immediately after treatment, and that the role of the drug was therefore possible.

These two explanations may well coexist: in some cases, the site may have become contaminated with *Pseudomonas aeruginosa* at dry-off (for example, during administration of the intramammary product), while in other cases, it may have occurred previously. In both cases, however, local reactions at the site related to the sudden cessation of milking (oedema, pain, loss of milk, etc.), combined with the intrinsic resistance of *Pseudomonas aeruginosa* to the antimicrobials used, allowed the proliferation of *Pseudomonas* at the site and the onset of peracute mastitis that in some cases was fatal.

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Following a request from one of the MA holders concerned about the possibility of classifying causality in these reports as "N", the French Commission for Veterinary Medicinal Products concluded at its meeting in October 2011 that when assessing causality of adverse events, consideration should be given to the role of treatment in the broader sense, therefore including the conditions of administration, and that such cases cannot be classified as "N-Unlikely". In addition, the French Commission for Veterinary Medicinal Products also requested that information on the possible onset of mastitis despite treatment be added to the SPC of all "dry cow" drugs.

Following this opinion, in 2012, ANSES-ANMV amended the SPC of all intramammary "dry cow" drugs authorised in France to include the following information in the "Special precautions for use in animals" section:

"The product's efficacy has only been established against the bacteria mentioned in the indications (Section 4.2). As a result, the onset after dry-off of a serious mastitis [that may be life-threatening] due to other bacteria, especially Pseudomonas aeruginosa*, remains a possibility.*

To reduce this risk, rules on asepsis must be strictly adhered to when administering the product; cows must also be monitored in the days following dry-off and should be kept in a hygienic environment away from the milking environment".

V – 3 Permethrin in cats

Permethrin is an antiparasitic authorised for dogs that can cause serious adverse events and even mortality in cats. This toxicity is related to cats' inability to eliminate certain compounds like permethrin. Affected cats mainly have neurological symptoms (tremors, seizures, ataxia, agitation, hyperaesthesia, coma) with or without digestive symptoms such as hypersalivation.
After examining the pharmacovigilance data, the CNPV, which had received a formal request from the ANMV, recommended in 2003 improving packaging readability for the contraindication related to 'cats'. It also suggested including additional statements on the adverse events likely to be observed in cats [*"can cause potentially fatal seizures"*] and measures to be taken in the event of adverse events in this species [*"Wash cat with shampoo or soapy water. Consult your veterinary practitioner quickly"*].

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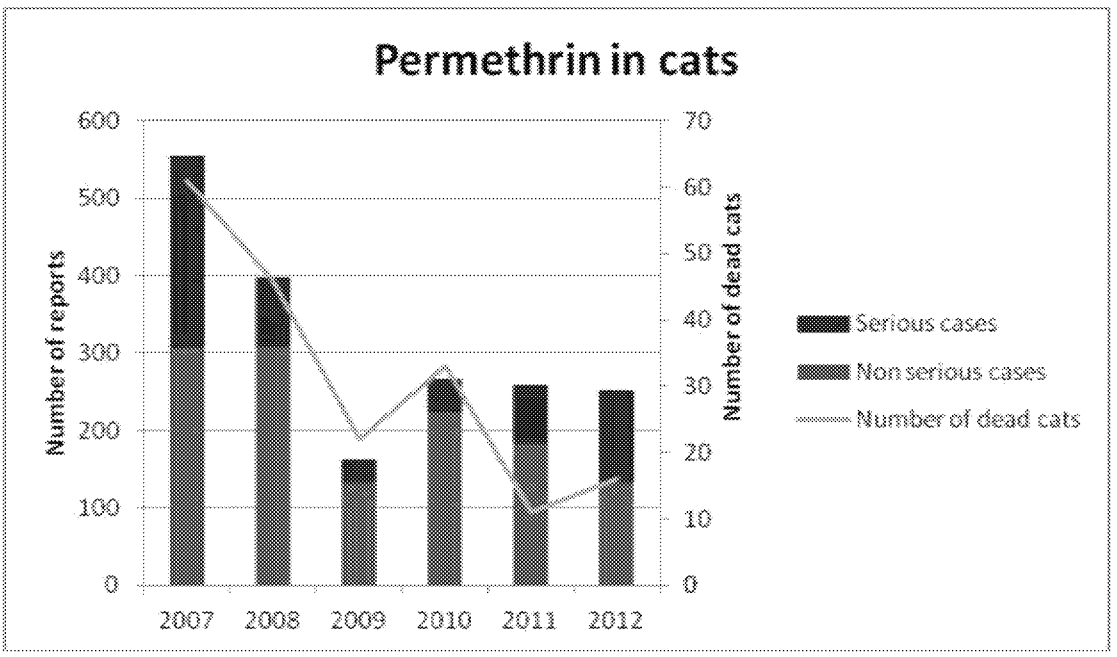

After the CNPV issued its opinion, a communication campaign was undertaken (see box in issue 2 of the Veterinary Pharmacovigilance newsletter and the ANMV press release of 11 July 2006) and decisions to automatically modify the marketing authorisations for the drugs in question were prepared by the ANMV, with new labelling rules in force as of January 2007.

From 2007, the number of reported cases began to fall. Between 2007 and 2009, the fall in sales volumes of the main drugs involved was not enough to explain the observed decrease in the number of cases reported during this period.

However, reports of adverse events in cats are still being recorded (258 in 2012, of which 121 were regarded as serious). As a reminder of the toxicity of permethrin-based antiparasitics to cats, ANSES-ANMV issued a new press release in June 2013.

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V – 4 Changes to MAs related to pharmacovigilance data and reported in 2012

FELIGASTRYL®: This concerns eserine tablets for the treatment of intestinal obstruction due to fur balls in cats. For this older drug (authorisation was issued in 1984), the SPC stated that the adverse effects were unknown. However, an assessment of a Periodic Safety Update Report covering a period of three years showed the recording of 15 reports of adverse events, including one serious case. The adverse events in these 15 reports mainly concerned agitation, hyperactivity, excitement or muscle tremors, with an incidence of about one case in 25,000 treated animals (incidence categorised as "very rare"). The ANMV therefore asked the MA holder to update the "Adverse reactions" section of the SPC for FELIGASTRYL®, which has now been amended as follows:
"In rare cases, neurological disorders such as hyperactivity, agitation and muscle tremors related to the anticholinesterasic properties of eserine may occur."

CALMIVET TABLETS® is a drug based on acepromazine used as a sedative in dogs and cats, especially in anticipation of long transport journeys, which is presented in the form of small tablets. In 2011, a review of poisonings in children due to veterinary drugs showed that this product was involved in three cases of poisoning (two accidental ingestions and one intentional), including two cases of "moderate" severity (drowsiness) and one serious case (Glasgow Coma Scale of 7).
The SPC has been amended as follows:

- on the packaging: *"Keep out of the reach and sight of children."*
- on the SPC, Section 4.5 ii: *"Do not let children play with the tablets. In the event of accidental ingestion of a tablet, contact your doctor immediately and show the package leaflet."*

CANILEISH®: for this vaccine against canine leishmaniasis, which obtained its MA according to the centralised procedure, France acts as rapporteur at European level and is therefore responsible for post-MA surveillance. After a year on the market, the pharmacovigilance data collected at European level have highlighted the possible occurrence following administration of skin necrosis reactions, some of which could be serious due to their extent or depth, requiring complicated local care or even surgery, and/or their association with systemic signs. The SPC for **CaniLeish®** has therefore been amended as follows:
"After injection, moderate and temporary local reactions may occur, such as oedema, nodules, pain on palpation or erythema. These reactions resolve spontaneously within 2 to 15 days. ***In very rare cases, a more serious reaction at the injection site (injection site necrosis, vasculitis) has been reported.*** *[...]".*

COXEVAC®: for this vaccine against Q fever, intended for cattle and goats and with an MA obtained according to the centralised procedure, France acts as rapporteur at European level and is responsible for post-MA surveillance. In 2011 and 2012, pharmacovigilance data showed cases of falling milk production in vaccinated goats, mainly in the Netherlands, leading to the culling of animals in the most serious cases. Consequently, on the recommendation of the CVMP, the SPC for COXEVAC® has been amended to include this risk specific to goats in the "Special precautions for use" section:

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"In field conditions, vaccination with Coxevac was frequently followed by a fall in milk production in goats. Care should be taken to reduce stress as much as possible during the administration of the product, since this contributes to this adverse effect."

CERTIFECT® also has a centralised MA for which France is the rapporteur. This is a spot-on antiparasitic containing fipronil, amitraz and S-methoprene, intended for the treatment and prevention of flea and tick infestations in dogs. The "Adverse reactions" section of the SPC mentions the classic adverse reactions to amitraz, and states that they can occur after licking the product. However, an analysis of the pharmacovigilance data revealed many cases of typical adverse reactions to amitraz in treated dogs, very few of which involved suspected or confirmed licking of the product. In 2012, the CVMP therefore recommended reformulating the wording of the SPC so as not to restrict the possible adverse reactions solely to cases where the dog has licked the product.
The MA holder has accepted this recommendation and has committed to submitting shortly an application to amend the SPC for CERTIFECT®.

ATOPICA 25mg/50mg/100mg®: ATOPICA (capsules) is a drug containing cyclosporine indicated for the treatment of chronic manifestations of atopic dermatitis in dogs. Analysis of pharmacovigilance data for this drug in 2012 revealed cases of diabetes mellitus in treated dogs, mostly Westies (West Highland white terriers) and mainly in the United Kingdom. As this breed is particularly at risk with regard to atopic dermatitis, it is not surprising to see it over-represented in cases of adverse events due to ATOPICA, and the existence of a real breed effect for this potential complication with diabetes mellitus cannot easily be confirmed. However, considering that this is a complication requiring the cessation or at least adaptation of treatment and appropriate care as early as possible, the "Adverse reactions" and "Special precautions for use in animals" sections of the SPC for ATOPICA capsules have respectively been supplemented with the following sentences:
"Very rare cases of diabetes have been observed, mainly in Westies (or West Highland white terriers)."
"In the event of the onset of diabetes after treatment with the product (e.g. polyuria or polydipsia), the dosage should be reduced or treatment ceased and a veterinarian should be consulted."

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VI – SPECIFIC ACTIONS IN 2012

Following the commitment made by ANSES-ANMV, special attention was paid to communication. Thus in 2012, in addition to the publication of its first annual report on veterinary pharmacovigilance, two press releases also drew prescribers' attention to medicinal products.

CLOSAMECTIN pour-on solution for cattle® is an antiparasitic based on ivermectin and closantel indicated for the treatment of mixed infestations in cattle. At the end of 2011 and during 2012, the ANMV received reports describing neurological symptoms in cattle treated with the doses recommended in the SPC, and without any licking being observed. These symptoms, including locomotor difficulties and ataxia, as well as sometimes irreversible loss of vision and feeding behaviour (anorexia) and digestive disorders (diarrhoea), are entirely consistent with the known toxicity of closantel in the event of overdose, but they nevertheless occurred in the absence of proven overdose. These cases, when related to the sales volumes for this drug, represent about one animal affected in 50,000 treated. These pharmacovigilance data were discussed with experts from the CNMV. Although the incidence is very rare, the severity of the signs led the ANMV, acting on the opinion of the CNMV, to quickly communicate with healthcare professionals in order to inform them and encourage reporting of such cases.
Moreover, after the reference Member State for this drug (the United Kingdom) had analysed the reports at European level, the SPC for CLOSAMECTIN POUR-ON was amended in 2012 to add the following information respectively to the "Adverse reactions" and "Special precautions for use in animals" sections:
"In very rare cases, neurological disorders such as blindness have been observed after administration of the product."
"Care must be taken to avoid overdosing in animals from the volume administered, accidental spillage of the product or oral ingestion, as an overdose can lead to toxicity symptoms such as lack of coordination and blindness.
Shearing of the animals before treatment should be avoided, so as to reduce the risk of increased absorption of the drug and therefore the bioavailability of the product, and the risk of oral ingestion following licking between animals."

SERESTO®: SERESTO collars are antiparasitic drugs based on flumethrin and imidacloprid, authorised for use in cats and dogs. These collars have been on the market in France since the beginning of 2012, and in the first six months of the year ANSES-ANMV recorded a series of non-serious events in cats and dogs.
As the MA holders are under no obligation to submit reports of non-serious cases to ANSES-ANMV as they are received (these reports are only brought to the attention of the authorities through PSURs), the reports already stored in the national database were unable to provide a comprehensive view of the situation. Accordingly, ANSES-ANMV asked the MA holder to quickly send it all the non-serious reports it had received directly and which had therefore not previously been brought to the attention of ANSES-ANMV.

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As a result, 149 additional non-serious cases were added to the data already stored in the national database.

An analysis by ANSES-ANMV and CPVL experts showed that the adverse events reported were mainly local reactions, occurring more frequently in cats (1 case in 374) than in dogs (1 case in 3030). The observed reactions corresponded to the adverse effects described in the leaflet (depilation, erythema, pruritus), but in very rare cases the local reaction observed was more severe (burns, ulcers). In dogs, the reported cases mainly concerned the product's suspected lack of efficacy with respect to ticks (1 case per 1691 dogs treated).

These pharmacovigilance data were discussed with experts from the CNMV and led to the publication of a press release to inform prescribing veterinarians.

Moreover, after the reference Member State for the drug (Germany) had analysed the reports at European level, the SPC for SERESTO collars was amended in the summer of 2013 to supplement the "Adverse reactions" section (changes are indicated in bold) as follows:

"Occasionally, mild behavioural disorders that may include scratching at the application site can be observed in animals not accustomed to wearing collars, during the first few days after it has been fitted. *Ensure that the collar is not too tight.*

Mild reactions at the application site such as pruritus, erythema or hair loss may occur. These reactions have rarely been reported in dogs and are uncommon in cats, and usually disappear within one or two weeks without having to remove the collar. *In some cases, the temporary removal of the collar may be recommended until the symptoms disappear.*

In very rare cases in dogs and rarely in cats, reactions such as dermatitis, inflammation, eczema or lesions may occur at the application site, and in these cases it is recommended to remove the collar.

In cats, in rare cases, mild and temporary reactions such as depression, change in food intake, salivation, vomiting and diarrhoea may occur at the beginning.

As with other topical applications, allergic contact dermatitis may occur in hypersensitive animals."

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VII - ADVERSE EVENTS IN HUMANS IN 2012

Adverse events in humans can occur through contact with treated animals, through direct contact with a veterinary medicinal product during administration to animals, or through mishandling, misuse or abuse of a veterinary medicinal product.
Any adverse event occurring in humans following the use of such a drug that is brought to the attention of a healthcare professional or an MA holder must be reported to ANSES-ANMV within 15 days of notification.
A few reports of adverse events in humans following the use of veterinary medicinal products are sent directly to ANSES-ANMV or the Veterinary Pharmacovigilance Centre in Lyon, but the vast majority of these cases are recorded by French poison control and monitoring centres (CAPTVs) via their emergency hotlines.
From the reports of human exposure recorded by the CAPTVs in 2012, all reports for that year relating to veterinary medicinal products, as classified in the National Database on products and compositions (BNPC) of the CAPTV information system, were extracted.
Reports of human exposure to veterinary medicinal products compiled by the CAPTVs are uncommon, accounting for only 0.6% of all reports in 2012, or 1190 cases. Of these 1190 recorded cases, adverse events were reported in 380 cases, i.e. 32%.

To these 380 cases of adverse events recorded by the human toxicovigilance network, 55 cases reported to the veterinary pharmacovigilance network should be added, making a total of 435 cases of adverse events in humans in 2012 due to the use of veterinary medicinal products.
These 435 cases of adverse events concerned at least 228 different veterinary drugs.

The main therapeutic categories involved in these 435 reports were antiparasitics (44%), vaccines (23%) and euthanasia drugs (4%). The remaining reports are divided among the various other therapeutic categories.

This breakdown reflects quite logically these products' conditions of use:

- Antiparasitics prove to be the most frequently implicated veterinary medicinal products. They are widely used in routine treatment for the animal population as a whole (not just sick individuals) and are also frequently administered by the owners themselves.
- Vaccines are in second place, essentially due to accidental injections. Although this is a category of products whose use potentially concerns all animals (due to its preventive and not curative aims), of the 101 veterinary vaccines mentioned, 98% are products intended for production livestock. This finding is unsurprising insofar as mass vaccination in industrial sectors is often carried out by farmers and not veterinarians.

The symptoms described were temporary and relatively benign forms of irritation: primarily skin, eye and/or respiratory signs with external antiparasitics, and inflammatory reactions with accidental injection.

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- Euthanasia drugs form a separate category. The adverse events occurring with this type of product most often affect the veterinarians themselves – or their close associates – through suicide attempts, because of their access to the products concerned.

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CONCLUSION

Veterinary medicinal products, like human drugs, are subject to European regulations. They are only granted marketing authorisation (MA) if an assessment of data on their quality, safety and efficacy concludes that the benefit associated with their use outweighs the risks.
This assessment process helps define the product's conditions of use in terms of destination species, therapeutic indication(s), treatment regimen, withdrawal period, contraindication(s), precaution(s) for use, etc., which are outlined in the summary of product characteristics (SPC) appended to the marketing authorisation. Of the 3197 veterinary medicinal products authorised in France, 97% now have an SPC which can be consulted on the ANSES website (http://www.ircp.anmv.Anses.fr/), and the goal for the end of 2013 is to provide this SPC for all authorised and marketed medicinal products. This information, validated by ANSES-ANMV or by the European Commission, is repeated on the labelling and/or instructions that accompany all medicinal products.
Nevertheless, even if a number of adverse reactions are listed on the SPC at the time the marketing authorisation is issued, when the product is used on a large scale and under real field conditions, pharmacovigilance can provide a better understanding of their nature, incidence and the possible risk factors associated with each veterinary medicinal product.

The effectiveness of the French veterinary pharmacovigilance scheme is based on spontaneous reports, which currently, in more than 90% of cases, are submitted by veterinarians.
Each report is recorded and assessed by both the MA holders concerned and the relevant authorities (ANSES-ANMV and the Veterinary Pharmacovigilance Centre in Lyon). This expert appraisal leads to a causality assessment being assigned to each of the drugs mentioned in the report, according to the ABON system, which characterises at a time "t" the probability of a causal link between the drug and the adverse event observed.

The result of this individual expert appraisal (for reports that were initially transmitted to ANSES-ANMV or the CPVL) is sent to the initial reporter via a response letter addressed to them personally.

Potential signs identified then undergo a collective assessment. This may take place at European level, with experts from the competent authorities of other European states and/or at national level, with experts from the French Commission for Veterinary Medicinal Products (CNMV).
The purpose of this surveillance is to detect any emerging sign as quickly as possible, whether it is an unexpected adverse event, or one that is expected but whose frequency or severity is unexpected, and then to take appropriate measures, which can range from modifying the SPC to suspending the MA.

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While ANSES-ANMV ensures the implementation of the national veterinary pharmacovigilance system, all MA holders are obliged to establish a pharmacovigilance system that meets their different regulatory requirements, especially in terms of recording, communicating and assessing any adverse events. In France, the companies with this responsibility are pharmaceutical establishments authorised by ANSES-ANMV as veterinary medicinal product "distributors" specially authorised for this activity. As such, they are also inspected regularly by ANSES-ANMV inspectors.
To date, 57 establishments now have this status of "distributors", and in accordance with the decisions made by the Director General of ANSES concerning frequency of inspections, 12 to 15 sites responsible for pharmacovigilance are inspected annually by the ANMV. Planning is adapted according to the risk analyses prepared after each inspection.
The results of the 2012 inspections show that the main areas for further improvement concern the processes relating to organisation of pharmacovigilance systems and quality management.

Moreover, as part of moves to improve the national pharmacovigilance system, ANSES-ANMV also undertook two actions with regard to MA holders. The first concerns the use of the European pharmacovigilance network, EudraVigilance. MA holders must transmit reports of all serious cases they are aware of to ANSES-ANMV, by electronic means, within 15 days. In March 2012, ANSES-ANMV therefore organised a new training course on the use of EudraVigilance. This session, based on practical exercises, brought together 13 participants from both French and foreign operators. This course was especially welcome since in Europe, France is the only country to offer this type of training.

To improve the quality of the data contained in the reports, ANSES-ANMV, in consultation with the SIMV, also posted online recommendations for MA holders to clarify the expectations of ANSES-ANMV with regard to the contents of certain data fields.

The results of the 2012 assessment show that the total number of reports continues to increase steadily. The results are generally comparable to those obtained in 2011 and confirm that the national system in place is fully capable of detecting new signs and thus supplement the available knowledge on veterinary medicinal products.

Following the previous report, ANSES-ANMV, in addition to its regular assessment activities, took a number of initiatives in terms of communication and promotion of pharmacovigilance in the industrial sectors.

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Communication on pharmacovigilance

In terms of communication, various studies have been conducted in collaboration with the French Commission for Veterinary Medicinal Products (CNMV).

Firstly, once validated, the minutes of the various CNMV meetings are quickly published on the ANSES website. These minutes systematically include information on the situation concerning serious cases reported since the last meeting, and may also contain information about one or more specific drugs. These particular items are prepared at the initiative of ANSES-ANMV or following an internal request from the CNMV. Following these special announcements, press releases were published in July 2012 on CLOSAMECTIN POUR-ON SOLUTION FOR CATTLE and on SERESTO collars, with the aim of informing prescribers. However, not all the drugs discussed by the CNMV systematically require specific action.

Moreover, since the beginning of the year, in addition to the decisions granting or withdrawing MA, ANSES-ANMV has been posting online amendments to SPCs that affect public health (for example, an extension of a withdrawal period, a restriction relating to species or indications, additional information resulting from pharmacovigilance data).

Lastly, the CNMV experts were also asked about general topics related to pharmacovigilance, such as for example an "operational" definition of serious non-fatal cases (see the CNMV opinion published in June 2013 on the ANSES website). Other discussions are also underway and details will be published shortly.

Actions relating to the production animals sectors

Given the low rate of reporting in the production animals sectors, specific actions have been undertaken by ANSES-ANMV to raise awareness among the veterinarians concerned. This included the presentation of a session on pharmacovigilance at the national days organised by the SNGTV (French National Society of Veterinary Technical Groups) in Nantes in May 2012. Based on actual cases, the presentation stimulated debate on the expert appraisal work and the difficulties encountered by both practitioners and ANSES-ANMV.

One of the difficulties for these sectors lies in the fact that, unlike pets, cattle or horses, for example, monitoring of animals is not individual but collective. Therefore, in order to more effectively take into account the adverse events affecting multiple animals, models of the reporting of adverse events are under review. This work, which was begun in 2012 in consultation with the rabbit sector of the SNGTV, is now underway with other production sectors.
Initial discussions with the stakeholders in these production animals sectors have revealed high expectations, not only in the field of pharmacovigilance but also more generally in the post-MA area, especially on the use and availability of drugs. The need to develop the post-MA area was also identified by the various inspection missions carried out at ANSES in 2011.

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To better meet these expectations and improve efficiency, ANSES-ANMV underwent a reorganisation and established a market surveillance unit in July 2013 within the inspection and market surveillance department. The missions of this unit include:

- health watch and management of information on medicinal products placed on the market, and monitoring of the availability of veterinary medicinal products;
- monitoring and management of quality defects in veterinary medicinal products;
- coordination of quality control of veterinary drugs already on the market or subject to an application for marketing authorisation (including the issue of counterfeiting);
- control of medicinal product advertising;
- monitoring of compliance of labelling and instructions for veterinary medicinal products;

In addition to this reorganisation, and in order to be able to continue to develop its communication and/or promotion activities, the pharmacovigilance department increased its headcount in early 2013. Two new recruits, including one person responsible for coordinating the pharmacovigilance networks, should enable the current efforts to be continued in terms of communication and promotion.

One of the priorities identified concerned the training of veterinarians. Actions have therefore been planned to raise awareness about pharmacovigilance among students of the four French veterinary schools. These actions, planned as part of the initial training of veterinarians, will be supplemented by the introduction of a module on pharmacovigilance in the continuing training proposed to veterinarians.

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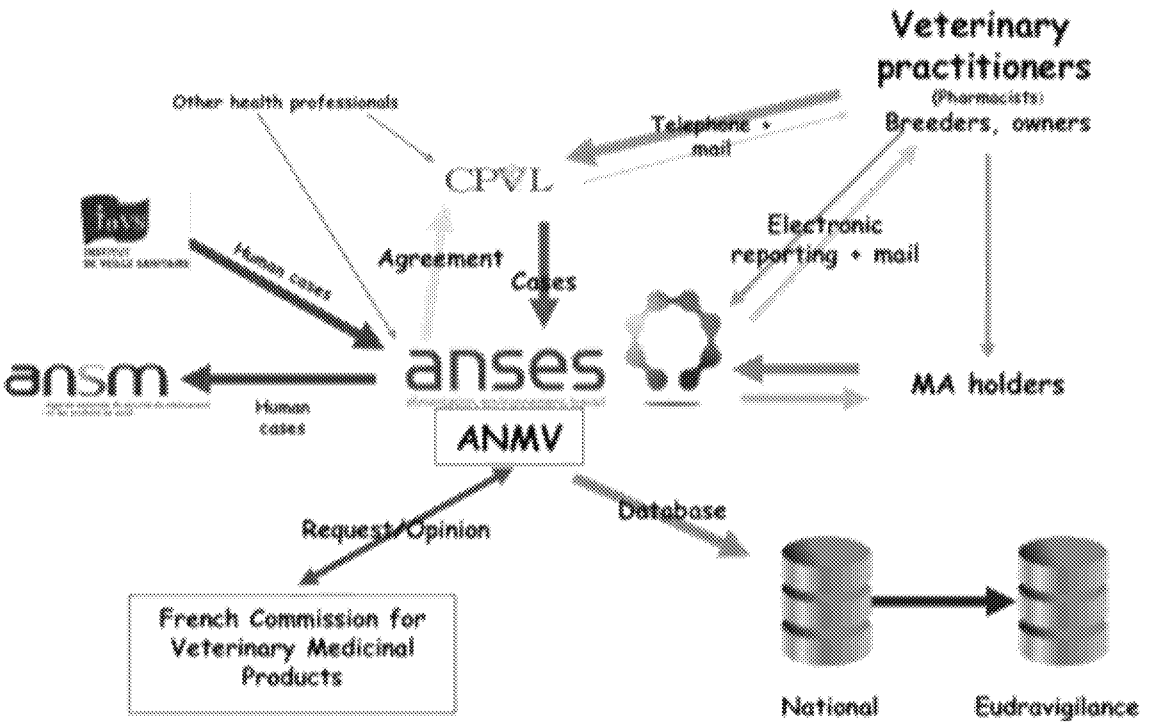
ANNEX 1 – THE FRENCH PHARMACOVIGILANCE SYSTEM

Adverse events are monitored under the French national veterinary pharmacovigilance system whose key operators are indicated below:



ANNEX 2 – THE METHOD FOR ASSESSING CAUSALITY OF ADVERSE EVENTS IN VETERINARY MEDECINE – THE ABON SYSTEM

All the available data, when compared with bibliographic data and previous recorded cases, result in a case being ranked in one of four categories of causality (A, B, O or N) as stipulated in the European Medicines Agency guidelines. It reflects the link between the medicinal product administered and the clinical signs observed:

- A (probable),
- B (possible),
- O1 (inconclusive),
- O (unclassifiable/unassessable),
- N (unlikely).

For assessing causality, the following factors should be considered:

1. Association in time – including the possible disappearance or recurrence of symptoms on discontinuation of treatment or during repeated administrations – or anatomical correspondence (especially with the site of injection or application of the medicinal product).
2. Pharmaco-toxicological profile, blood levels, and experience of the medicinal product.
3. Presence of characteristic clinical or pathological phenomena.
4. Exclusion of other possible causes.
5. Completeness and reliability of the data in the case reports.
6. Quantitative measurement of the degree of contribution of a medicinal product to the development of an adverse event (dose-effect relationship).

For inclusion in category "A" (Probable), it is recommended that all the following minimum criteria should be complied with:

- there should be a reasonable association in time between the administration of the veterinary medicinal product and the onset and duration of the reported event.
- the description of the clinical phenomena should be consistent, or at least plausible, given the known pharmacology and toxicology of the product.
- there should be no other equally plausible and remotely pertinent explanation(s) of the case. (If one or more are suggested, however, are they validated? What is their degree of certainty?) In particular, concurrent use of other products (and possible interactions) or intercurrent disease should be taken into account in the assessment.

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Where any of the above criteria cannot be satisfied (due to conflicting data or lack of information), then such reports can only be categorised as "B" (Possible), "N" (Unlikely), or "O" (Unclassifiable/Unassessable).

For inclusion in category "B" (Possible), it is recommended that this be applied when medicinal product causality is one of several plausible causes for the described event, but where the available data do not meet all of the criteria for inclusion in category "A".

For inclusion in category "O1" (Inconclusive), all cases where a link with the medicinal product cannot be excluded but where other factors preclude reaching a conclusion.

For inclusion in category "O" (Unclassifiable/Unassessable), all cases where reliable data on the adverse events are unavailable or insufficient to assess causality.

For inclusion in category "N" (Unlikely), cases where sufficient information exists to establish beyond reasonable doubt that an alternative cause independent of the medicinal product can explain the reported event.

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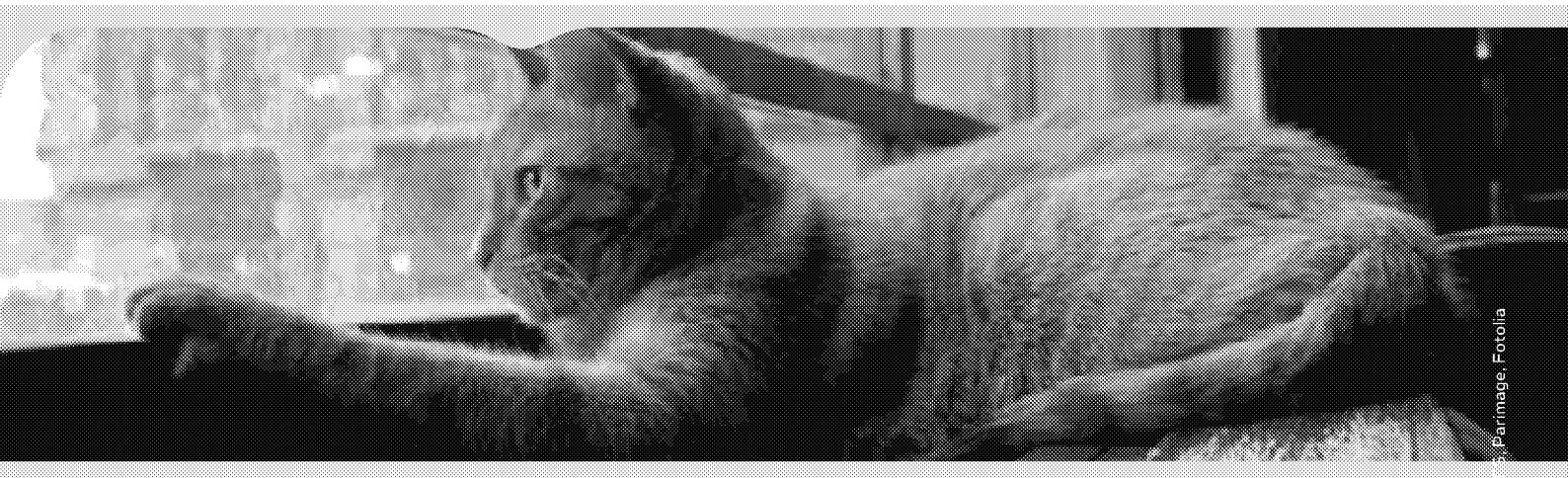

French Agency for Food,
Environmental and Occupational Health & Safety
27-31 avenue du général Leclerc
94701 Maisons-Alfort Cedex
www.anses.fr

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Seresto 1.25 g + 0.56 g, collar for cats [AT, BE, CY, DE, DK, EL, ES, FI, FR, IE, IS, IT, LU, NL, NO, PT, SE, UK]
Foresto 1.25 g + 0.56 g, collar for cats [BG, CZ, EE, HU, LT, LV, PL, RO, SK, SI]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:

One collar of 38 cm (12.5 g) contains 1.25 g imidacloprid and 0.56 g flumethrin as active substances.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Collar
Grey, odour free collar.

4. CLINICAL PARTICULARS

4.1 Target species

Cats

4.2 Indications for use, specifying the target species

For the treatment and prevention of flea (*Ctenocephalides felis)* infestation for 7 to 8 months.
Protects the animal's immediate surroundings against flea larvae development for 10 weeks.
Seresto can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD).

The product has persistent acaricidal (killing) efficacy (*Ixodes ricinus, Rhipicephalus turanicus)* and repellent (anti-feeding) efficacy against tick infestations (*Ixodes ricinus)* for 8 months. It is effective against larvae, nymphs and adult ticks.
Ticks already on the cat prior to treatment may not be killed within 48 hours after collar application and may remain attached and visible. Therefore removal of ticks already on the cat at the time of application is recommended. The prevention of infestations with new ticks starts within two days after application of the collar.

4.3 Contraindications

Do not treat kittens less than 10 weeks of age.
Do not use in case of hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings for each target species

Ticks will be killed and fall off the host within 24 to 48 hours after infestation without having had a blood meal, as a rule. An attachment of single ticks after treatment cannot be excluded. For this reason, a transmission of infectious diseases by ticks cannot be completely excluded if conditions are unfavourable.
Ideally, the collar should be applied before the beginning of the flea or tick season.

As in all longterm topical products, periods of excessive seasonal hair shedding may lead to transient slight reduction of efficacy by loss of hair-bound portions of the active ingredients. Replenishment from the collar starts immediately so that full efficacy will be re-established without any additional treatment or collar replacement. For optimum control of flea problems in heavily infested households it may be necessary to treat the environment with a suitable insecticide.

The product is water resistant; it remains effective if the animal becomes wet. However, prolonged, intense exposure to water or extensive shampooing should be avoided as the duration of activity may be reduced. Studies show that monthly shampooing or water immersion does not significantly shorten the 8 months efficacy duration for ticks after redistribution of the active substances in the coat whereas the product's flea efficacy gradually decreased, starting in the 5th month.

4.5 Special precautions for use

Special precautions for use in animals

Not applicable.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Keep the bag with the collar in the outer packaging until use.
As with any veterinary medicinal products, do not allow small children to play with the collar, or to put it into their mouths. Pets wearing the collar should not be allowed to sleep in the same bed as their owners, especially children.
People with known hypersensitivity to the ingredients of the collar should avoid contact with the veterinary medicinal product.
Immediately dispose of any remnants or cut-offs of the collar (see section 4.9).
Wash hands with cold water after fitting the collar.

4.6 Adverse reactions (frequency and seriousness)

In rare cases mild behavioural disorders that may include scratching at the application site may be observed in animals that are not used to wearing collars on the first few days after fitting. Ensure that the collar is not fitted too tightly.
Mild application site reactions such as pruritus, erythema and hair loss may occur. These have been reported as uncommon and usually resolve within 1 to 2 weeks without the need for collar removal.
In single cases, a temporary collar removal may be recommended until the symptoms have disappeared.
In rare cases, application site reactions such as dermatitis, inflammation, eczema or lesions may occur and in these instances, collar removal is recommended.
Also in rare cases, slight and transient reactions as depression, change of food intake, salivation, vomiting and diarrhoea might occur initially. As in other topical applications, allergic contact dermatitis might occur in hypersensitive animals.

The frequency of adverse reactions is defined using the following convention:
very common (affects more than 1 animal in 10)
common (affects 1 to 10 animals in 100)
uncommon (affects 1 to 10 animals in 1,000)
rare (affects 1 to 10 animals in 10,000)
very rare (affects less than 1 animals in 10,000)

4.7 Use during pregnancy, lactation or lay

Laboratory studies with either flumethrin or imidacloprid in rats and rabbits have not produced any effects on fertility or reproduction and showed no teratogenic, or foetotoxic effects. However, the safety of the veterinary medicinal product has not been established in target animals during pregnancy and lactation and in the absence of available data, the product is therefore not recommended in pregnant and lactating queens.

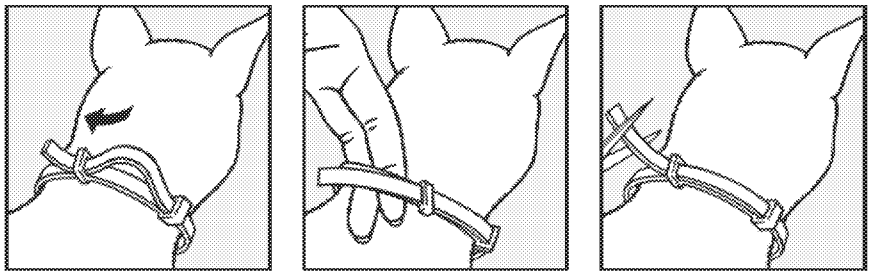
4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

Cutaneous use. One collar per animal to be fastened around the neck.
Cats receive one collar of 38 cm length.
For external use only.

Remove collar from protective bag directly before use. Unroll collar and make sure that there are no remnants from the plastic connectors inside the collar. Adjust the collar around the animal's neck without tightening it too tight (as a guide, it should be possible to insert 2 fingers between the collar and the neck). Pull excess collar through the loop and cut off any excess length extending beyond 2 cm.



The collar should be worn continuously for the 8 month protection period and should be removed after the treatment period. Check periodically and adjust fit if necessary, especially when kittens are rapidly growing.

This collar is designed with a safety-closure mechanism. In the unlikely event of a cat being trapped, the cats own strength is sufficient to widen the collar to allow for quick release.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Due to the nature of the collar overdosage is unlikely and signs of overdosage are not to be expected.
An overdosage of 5 collars around the neck was investigated in adult cats for an 8 months period and in 10 week old kittens for a 6 months period and no other adverse effects were observed than already described in section 4.6.
In the unlikely event of the animal eating the collar mild gastrointestinal symptoms (e.g. loose stool) may occur.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: ectoparasiticides, insecticides and repellents, pyrethrins and pyrethroids, Flumethrin combinations
ATCvet code: QP53AC55

5.1 Pharmacodynamic properties

Imidacloprid is an ectoparasiticide belonging to the chloronicotinyl group of compounds. Chemically, it can be classified as a chloronicotinyl nitroguanidine.
Imidacloprid is active against larval flea stages, adult fleas and lice. Activity against *C.felis* starts immediately after application of the collar.
In addition to the indications listed under section 4.2 an activity against *Ctenocephalides canis* and *Pulex irritans* fleas has been demonstrated.
Imidacloprid has a high affinity for the nicotinergic acetylcholine receptors in the post-synaptic region of the central nervous system (CNS) of the flea. The ensuing inhibition of cholinergic transmission in insects results in paralysis and death. Due to the weak nature of the interaction with mammalian nicotinergic receptors and the postulated poor penetration through the blood-brain barrier in mammals, it has virtually no effect on the mammalian CNS. Imidacloprid has minimal pharmacological activity in mammals.

Flumethrin is an ectoparasiticide of the synthetic pyrethroid group. According to current knowledge the synthetic pyrethroids interfere with the sodium channel of nerve cell membranes, resulting in a delay in repolarization of the nerve and finally killing of the parasite. In studies on structure-activity relationship of a number of pyrethroids interference with receptors of a certain chiral conformation was noted thereby causing a selective activity on ectoparasites. No anti-cholinesterase activity was noted with these compounds. Flumethrin is responsible for the product's acaricidal activity and also prevents production of fertile eggs by its lethal effect on female ticks. In an *in-vitro* study 5 to 10 % of *Rhipicephalus sanguineus* ticks exposed to a sublethal dose of 4 mg flumethrin/L laid eggs which had a modified appearance (shrivelled, dull and dry) indicating a sterilising effect.

In addition to the indications listed under section 4.2 activity against *Ixodes hexagonus* and the non-European tick species *Amblyomma americanum* has been demonstrated.

The product provides repellent (anti-feeding) activity against the claimed ticks, thus preventing repelled parasites from taking a blood meal and thereby indirectly aids in the reduction of the risk of Vector-Borne Disease transmission. Indirect protection against the transmission of *Cytauxzoon felis* (transmitted by *Amblyomma americanum* ticks) has been shown in one laboratory study in a small number of animals at one month after treatment, thereby reducing the risk of diseases caused by this pathogen under the conditions of this study.

5.2 Pharmacokinetic particulars

Both active ingredients are slowly and continuously released in low concentrations from the polymer matrix system of the collar towards the animal. Both actives are present in the cat's haircoat in acaricidal/insecticidal concentrations during the entire efficacy period. The active substances spread from the site of direct contact over the entire skin surface. Target animal overdose and serum kinetic studies have established that imidacloprid reached the systemic circulation transiently while flumethrin was mostly not measurable. Oral absorption of both active substances is not relevant for the clinical efficacy.

5.3 Environmental properties

See section 6.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Titanium dioxide (E 171)
Iron oxide black (E 172)
Dibutyladipate
Propylene glycol dicaprylocaprate
Epoxidised soybean oil
Stearic acid
Polyvinyl chloride

6.2 Incompatibilities

None known.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 4 years

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Box containing one single 38 cm polyvinyl chloride based collar packed into a PETP/PE bag.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.
This product should not enter water courses as it may be dangerous for fish and other aquatic organisms.

7. MARKETING AUTHORISATION HOLDER

Bayer plc
Animal Health Division
Bayer House
Strawberry Hill
Newbury
Berkshire
RG14 1JA

8. MARKETING AUTHORISATION NUMBER

Vm 00010/4173

9. DATE OF FIRST AUTHORISATION

08 September 2011

10 DATE OF REVISION OF THE TEXT

June 2016

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

08 June 2016

Veterinary
Medicines
Directorate

Woodham Lane, New Haw, Addlestone, Surrey KT15 3LS
Telephone +44 (0)1932 336911 Fax +44 (0)1932 336618

Post Authorisation Assessments

[SHAPE * MERGEFORMAT]

Seresto 1.25 g + 0.56 g. Collar for Cats

•	08 June 2016	Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH.
•	08 June 2016	Renewal – UK as CMS.
•	13 May 2015	Change in the name of the manufacture of the active substance. Minor change to the test procedure of the active substance.
•	15 February 2015	Addition of specification parameters.
•	28 November 2014	Assessment of revised product literature.
•	14 May 2014	To include new therapeutic indications into the SPC/packaging information of Seresto in relation to the prevention of the transmission of Feline Vector Borne Diseases in cats.
•	16 April 2014	Change to marketing authorisation holder in France only from Bayer Santé to Bayer Healthcare.
•	07 February 2014	Significant change to the SPC regarding claim for use.
•	11 December 2013	Extension of shelf of the product as packaged for sale from 30 months to 48 months.
•	07 June 2013	Changes to section 4.6 Adverse Reactions of the SPC.

Message

From: Godfrey, Victoria (HC/SC) [victoria.godfrey@canada.ca]
Sent: 7/18/2016 12:42:43 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]
CC: Bruce, Dana (HC/SC) [dana.bruce@canada.ca]
Subject: PMRA Review of Seresto Incidents
Attachments: PMRA Seresto Review FINAL.docx

Hello all,

We confirmed with Bayer Canada that we can share our final review of the Seresto incidents. Bayer Canada does have a copy of the review, however, please keep in mind that it should not be shared outside of the EPA.

Thanks

Vicky

Victoria Godfrey

Incident Reporting Analyst, Incident Reporting Program
Pest Management Regulatory Agency/Government of Canada
victoria.godfrey@canada.ca/613-736-3769

Analyste, déclaration des incidents, Programme de déclaration d'incident
Agence de réglementation de la lutte antiparasitaire/Gouvernement du Canada
victoria.godfrey@canada.ca/613-736-3769

Message

From: Miller, David [Miller.DavidJ@epa.gov]
Sent: 2/16/2016 1:30:07 PM
To: Recore, Shanna [Recore.Shanna@epa.gov]; Evans, Elizabeth [Evans.Elizabeth@epa.gov]; Nguyen, James [Nguyen.James@epa.gov]; Sarkar, Bayazid [Sarkar.Bayazid@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Breeden, Julie [Breeden.Julie@epa.gov]
Subject: Fw: Az. 304.30502.0.135334 - Question on reported incidents associated with Seresto dog collar

FYI - response from Germany re: Seresto collar.

I thought we were told by Bayer early on in this process that the Seresto collar started out prescription only in Europe but is now OTC. Looks like for cats it remains prescription only because one of the the ai's is new, but for dogs both ai's are not new and well known so the collar was therefore given OTC status from the beginning.

Bottom line is that while the German BVL cannot send us the PSUR on Seresto due to confidentiality, they don't seem to be too concerned with the incident reports - or are at least not letting us know they are in the info they provide below

_____
From: Reimer, Inke <inke.reimer@bvl.bund.de>
Sent: Tuesday, February 16, 2016 3:51 AM
To: Miller, David
Cc: TAMReg; Ref. 304; Abt. 3; Wedemeyer, Manuel; Kirsch, Dr. Katrin
Subject: Az. 304.30502.0.135334 - Question on reported incidents associated with Seresto dog collar

Dear David,

I am sorry that I cannot send you any assessment reports on periodic safety update reports (PSUR) of Seresto because of obligations to confidentiality.

I was a little bit astonished about the information that the "collar was moved from veterinary prescription (only) to over-the-counter sales". In Europe there are 4 Seresto collars authorized: one for cats, one for cats and dogs, one for small dogs (<8kg), and one for large dogs (>8kg). In Germany, the two collars for cats are available on veterinary prescription only because flumethrin was a new active ingredient for the cat at the time of the authorization procedure. For dogs, both active ingredients were well known, therefore the collars for dogs are available over-the-counter (in Germany: available only in pharmacies). This status has not change since the authorization for Seresto collars has been granted. Prescription / nonprescription is a national issue in Europe, so this may be different in other member states.

There are some adverse event reports with Seresto collars involved. Most of the reports are non-serious; the animals often show pruritus, erythema and loss of hair at the application site. In rare cases dermatitis, inflammation, eczema or lesions develop. In cats in rare cases transient symptoms as depression, salivation, emesis or diarrhea may occur. Contact allergy in sensible individuals is possible. All these symptoms are already described as adverse events in the SPC.

I hope this answers your question at least a little bit.

Kind regards,
Inke

Inke Reimer
Bundesamt für Verbraucherschutz
und Lebensmittelsicherheit (BVL)
Abt. 3 Tierarzneimittel
Ref. 304 Postmarketing
Mauerstr. 39-42
10117 Berlin

E-Mail: inke.reimer@bvl.bund.de
Tel.: +49 (0)3018 445-7423
Fax: +49 (0)3018 444-89999

-----Ursprüngliche Nachricht-----

Von: BVL Kontaktformular [mailto:bvl.kontakt@noreply.bund.de <mailto:bvl.kontakt@noreply.bund.de>]

Gesendet: Montag, 8. Februar 2016 18:49

An: Poststelle BVL

Betreff: Question on reported incidents associated with Seresto dog collar

Salutation: Herr

First name : David

Name: Miller

Company: U.S Environmental Protection Agency

Street:

Zip: 20461

Town: Washington, DC

Telephone: +1 703 305 5352

Email: miller.davidj@epa.gov <mailto:miller.davidj@epa.gov>

Subject: Question on reported incidents associated with Seresto dog collar

Message: My name is David Miller and I am a branch chief in the US Environmental Protection Agency's Office of Pesticide Programs of a branch which deals with toxicovigilance issues associated with pet products. We are working closely the Canada's Pest Management Regulatory Agency which is working to determine whether to approve the registration of Bayer Animal Health's Seresto flea and tick collar for dogs and cats (U.S. EPA Registration Number 11556-155) containing the active ingredients flumethrin and imidacloprid. One aspect of this work is the investigation of reported incidents potentially associated with these collars.

We contacted EMA re: the recent approval of the collar to move from veterinary prescription (only) to over-the-counter sales and they suggested we contact BVL. I wondered if you had any information or reports on incidents that may be associated with this product that you might be willing to make available to us or any reports or analyses that you may have done to approve the re-designation of this product to an over-the-counter sales use.

Thank you for any assistance you may be able to provide.

Regards,

David.

Message

From: Biscoe, Melanie [Biscoe.Melanie@epa.gov]
Sent: 7/11/2016 1:34:10 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Adler, Bonnie [Adler.Bonnie@epa.gov]
Subject: RE: RE: IRR and ROR calculation update

Thank you Marietta!

Melanie Biscoe
Team Leader, Risk Management and Implementation Branch V
Pesticide Re-evaluation Division
Office of Pesticide Programs, US EPA
biscoe.melanie@epa.gov
703-305-7106

From: Echeverria, Marietta
Sent: Monday, July 11, 2016 8:17 AM
To: Arrington, Linda <Arrington.Linda@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Adler, Bonnie <Adler.Bonnie@epa.gov>
Subject: FW: RE: IRR and ROR calculation update

From: Miller, David
Sent: Friday, July 08, 2016 11:05 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>
Cc: OPP HED TEB <OPP_HED_TEB@epa.gov>; Nguyen, James <Nguyen.James@epa.gov>; Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>; Britton, Cathryn <Britton.Cathryn@epa.gov>; Waleko, Garland <Waleko.Garland@epa.gov>
Subject: FW: RE: IRR and ROR calculation update

All,

Please see the attached from Bayazid. This incorporates the sales data we received from Bayer on Thursday of last week. Note that Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Note that this only looks at data from 2014 and 2015 and – in this way – tends to (presumably) Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Some things to note:

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

David.

David J. Miller CAPT | USPHS
Chief, Chemistry & Exposure Branch
and Acting Chief, Toxicology & Epidemiology Branch
Health Effects Division
Office of Pesticide Programs
703-305-5352 (voice)
703-305-5147 (fax)

Visit www.epa.gov/pesticides

From: Sarkar, Bayazid
Sent: Tuesday, July 05, 2016 5:16 PM
To: Miller, David <Miller.DavidJ@epa.gov>
Cc: Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: RE: IRR and ROR calculation update

SAS code has been added as an appendix.
Thanks
Bayazid

From: Miller, David
Sent: Tuesday, July 05, 2016 5:10 PM
To: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>
Cc: Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: RE: IRR and ROR calculation update

Ok. Tx. Please add in the SAS code and output to this MS Word document, but do NOT include the MS excel sheet with the data.

From: Sarkar, Bayazid
Sent: Tuesday, July 05, 2016 4:59 PM
To: Miller, David <Miller.DavidJ@epa.gov>
Cc: Recore, Shanna <Recore.Shanna@epa.gov>
Subject: RE: IRR and ROR calculation update

Hi David,
I have attached draft updated IRR and ROR calculation based on most recent Bayer sales and incident data. I have used combined two year 2014 and 2015 data for this analysis. I excluded 'advantage topical solution' from this analysis because it has missing sales data for most of the quarters from 2014-2015. For IRR calculation I used pet month as offset which is the product of sales volume and life-cycle (i.e. for seresto it is 8 months and for spot on 1 month).
Thanks
Bayazid Sarkar

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 4/27/2016 6:09:37 PM
To: Miller, David [Miller.DavidJ@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Breeden, Julie [Breeden.Julie@epa.gov]
Subject: FW: Noteworthy NPIC incidents - Another Seresto Pet Incident
Attachments: 2016_3159.pdf

Everyone -

Here is another document outlining a Seresto incident.

-----Original Message-----
From: Miller, Robert
Sent: Wednesday, April 27, 2016 1:31 PM
To: Eagle, Venus <Eagle.Venus@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>
Subject: FW: Noteworthy NPIC incidents - Another Seresto Pet Incident

-----Original Message-----
From: Rivera-Lupianez, Ana
Sent: Wednesday, April 27, 2016 1:24 PM
To: Crowley, Matthew <Crowley.Matthew@epa.gov>; Miller, Robert <Miller.Robert@epa.gov>; Panger, Melissa <Panger.Melissa@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>; Gayoso, Jose <Gayoso.Jose@epa.gov>; Isbell, Diane <Isbell.Diane@epa.gov>; Chen, Jonathan <Chen.Jonathan@epa.gov>
Cc: Dumas, Richard <Dumas.Richard@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Hopkins, Yvette <Hopkins.Yvette@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: FW: Noteworthy NPIC incidents

Hi,

FYI
Another Seresto collar incident.

Thanks,
Ana

-----Original Message-----
From: Kaci Buhl [mailto:buhlk@ace.orst.edu]
Sent: Wednesday, April 27, 2016 12:48 PM
To: Rivera-Lupianez, Ana <Rivera-Lupianez.Ana@epa.gov>
Cc: Marcus, Craig <Craig.Marcus@oregonstate.edu>
Subject: Noteworthy NPIC incidents

Hello Ana,

We had a noteworthy case reported recently, and it met the criteria for referral to EPA because of the ongoing inquiry into Seresto products.

Case 2520 (Seresto Pet Collars): A person emailed NPIC reporting his cat's adverse reaction to a Seresto Pet Collar. Pictures were provided; see pages 3-4. As is the case for many emails, complete scenario information was not provided.

Thanks for your time,
--
Kaci Buhl, MS
Project Coordinator
National Pesticide Information Center
Oregon State University
Department of Environmental & Molecular Toxicology
(541) 737-8330
buhlk@ace.orst.edu
****

npic
NATIONAL PESTICIDE INFORMATION CENTER

2016 REFERRAL TO EPA **LOG: 3159**

Date: **April 25, 2016**

City, State: **Unknown**

Narrative:
Email Received:
Hello,
We have a huge problem, with a collar against flea and tick, Seresto collar.
Our cat (9 months old) made a very severe reaction, his back is completely burnt, and he has no hair anymore.
We need help, the laboratory Bayer we called, doesn't seem to hear us.
We would like to let the customers know about this possible huge effect.
We had a lot of medical invoice from the vet and we don't know, how many time it takes to come back normal.
I send you pictures.
Hope you can give us, a contact who is in charge of side effects because of a vet product which sells everywhere.
Thank you for your attention.
Bests regards

Email Response:
Thank you for emailing and reporting an adverse health effect to a pesticide. I am very sorry to hear about the situation with your cat. If he is still experiencing symptoms, you may consider contacting your pet's regular veterinarian or one of the animal poison control centers listed below.

ASPCA Animal Poison Control Center at 1-888-426-4435 ($65.00 credit card fee)
VET PETS at 1-800-572-5842 ($45.00 credit card fee)
Pet Poison Helpline at 1-800-213-6680 ($39.00 credit card fee)

Please call us at 800-858-7378 Monday - Friday from 8:00 am - 12:00 pm PT and speak directly to a Pesticide Specialist to further report and discuss the situation. In order to complete your report, we need to identify the specific product. Please have the EPA registration number or the active ingredient(s) available when you call. This information is specific to each product and located on the label. If you no longer have the package, you might consider visiting or contacting the retail store from which it was purchased to obtain this information.

The National Pesticide Information Center at Oregon State University is an information service and has no regulatory authority in relation to pesticides. However, our incident reports are made available to the U.S. EPA. Furthermore, our website features a reporting database that veterinarians can use to report adverse effects related to pesticide products. Please be aware this resource is only for veterinarians. Please consider encouraging your veterinarian to submit a report through this portal when they observe adverse reactions to pesticide products. The link for this portal is provided below.

npic
NATIONAL PESTICIDE INFORMATION CENTER

2016 REFERRAL TO EPA **LOG: 3159**

Veterinary Pesticide Adverse Effects Reporting
http://npic.orst.edu/vet

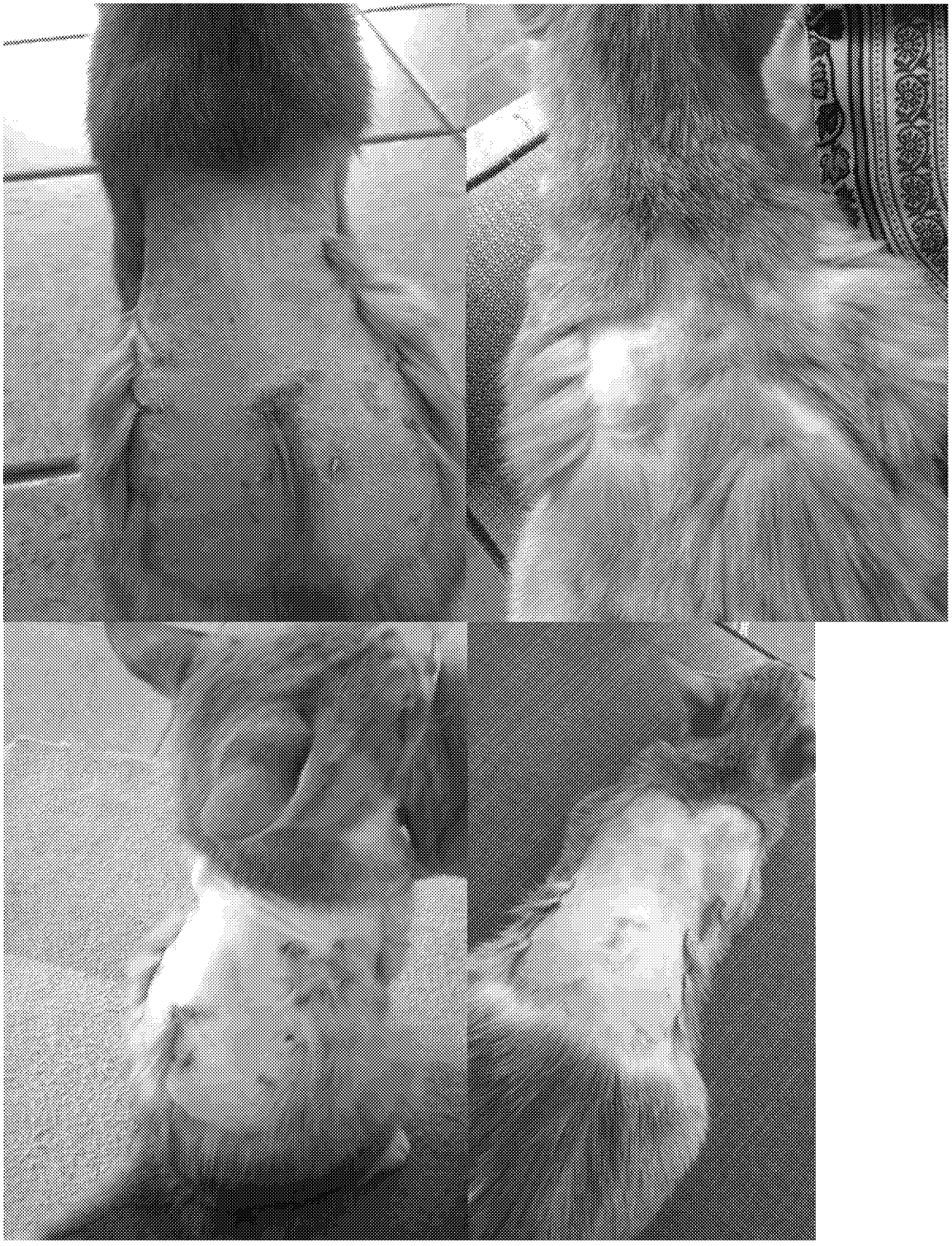
An additional mode of reporting adverse effects is by contacting the manufacturer. Under FIFRA 6(a)(2), manufacturers are required to submit adverse effects information about their products to the U.S. EPA. From your email, it sounds like the manufacturer may have been Bayer - Bayer appears to have a phone number specifically for their Bayer Animal Health division. If you haven't contacted them directly, you may consider calling them to report this issue. Their number, as well as additional manufacturer contact information can be accessed from the following link (alphabetical order):
http://npic.orst.edu/ingred/manuf.htm

Again, please contact us at 800-858-7378, Monday - Friday from 8:00am to 12:00pm PT. We look forward to answering any questions you have, and documenting your situation further.

****
Possible product information (per NPIRS database): active ingredient flumethrin and imidacloprid.
Inquirer sent follow up email with photos of cat's hair loss; no further incident details provided.
Provided information to EPA, Executive Committee and Project Coordinator.

npic
NATIONAL PESTICIDE INFORMATION CENTER

2016 REFERRAL TO EPA **LOG: 3159**



npic
NATIONAL PESTICIDE INFORMATION CENTER

2016 REFERRAL TO EPA **LOG: 3159**

Message

From: Miller, David [Miller.DavidJ@epa.gov]
Sent: 7/8/2016 4:07:32 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]
CC: OPP HED TEB [OPP_HED_TEB@epa.gov]; Nguyen, James [Nguyen.James@epa.gov]; Sarkar, Bayazid [Sarkar.Bayazid@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Britton, Cathryn [Britton.Cathryn@epa.gov]; Waleko, Garland [Waleko.Garland@epa.gov]
Subject: RE: RE: IRR and ROR calculation update

Ex. 5 Deliberative Process (DP)

David.

From: Miller, David
Sent: Friday, July 08, 2016 11:05 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>
Cc: OPP HED TEB <OPP_HED_TEB@epa.gov>; Nguyen, James <Nguyen.James@epa.gov>; Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>; Britton, Cathryn <Britton.Cathryn@epa.gov>; Waleko, Garland <Waleko.Garland@epa.gov>
Subject: FW: RE: IRR and ROR calculation update

All,

Please see the attached from Bayazid. This incorporates the sales data we received from Bayer on Thursday of last week. Note that Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Note that this only looks at data from 2014 and 2015 and – in this way – tends to (presumably) Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Some things to note:

- Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

David.

David J. Miller CAPT | USPHS
Chief, Chemistry & Exposure Branch
and Acting Chief, Toxicology & Epidemiology Branch
Health Effects Division
Office of Pesticide Programs
703-305-5352 (voice)
703-305-5147 (fax)

Visit www.epa.gov/pesticides

From: Sarkar, Bayazid
Sent: Tuesday, July 05, 2016 5:16 PM
To: Miller, David <Miller.DavidJ@epa.gov>
Cc: Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: RE: IRR and ROR calculation update

SAS code has been added as an appendix.
Thanks
Bayazid

From: Miller, David
Sent: Tuesday, July 05, 2016 5:10 PM
To: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>
Cc: Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: RE: IRR and ROR calculation update

Ok. Tx. Please add in the SAS code and output to this MS Word document, but do NOT include the MS excel sheet with the data.

From: Sarkar, Bayazid
Sent: Tuesday, July 05, 2016 4:59 PM
To: Miller, David <Miller.DavidJ@epa.gov>
Cc: Recore, Shanna <Recore.Shanna@epa.gov>
Subject: RE: IRR and ROR calculation update

Hi David,
I have attached draft updated IRR and ROR calculation based on most recent Bayer sales and incident data. I have used combined two year 2014 and 2015 data for this analysis. I excluded 'advantage topical solution' from this analysis because it has missing sales data for most of the quarters from 2014-2015. For IRR calculation I used pet month as offset which is the product of sales volume and life-cycle (i.e. for seresto it is 8 months and for spot on 1 month).
Thanks
Bayazid Sarkar

Message

From: Adler, Bonnie [Adler.Bonnie@epa.gov]
Sent: 4/27/2016 8:17:22 PM
To: Arrington, Linda [Arrington.Linda@epa.gov]; Atwood, Donald [Atwood.Donald@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Britton, Wade [Britton.Wade@epa.gov]; Cook, Colwell [cook.colwell@epa.gov]; Craig, Evisabel [Craig.Evisabel@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; English, LisaRenee [English.LisaRenee@epa.gov]; Hanson, Charmaine [Hanson.Charmaine@epa.gov]; Hawkins, Monica [Hawkins.Monica@epa.gov]; Holmes, Jean [Holmes.Jean@epa.gov]; VanAlstine, Julie [VanAlstine.Julie@epa.gov]; White, Katrina [White.Katrina@epa.gov]
Subject: Flumethrin DER for Seresto Collar
Attachments: MRID 48240140 DER.pdf

Per Doug's note below, see the DER by Byron Backus.
Thanks!
Bonnie

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Wednesday, April 27, 2016 4:13 PM
To: Adler, Bonnie <Adler.Bonnie@epa.gov>
Cc: Bruce Martin <bruce.martin@bayer.com>; Davis, Kable <Davis.Kable@epa.gov>; Britton, Wade <Britton.Wade@epa.gov>
Subject: RE: Flumethrin conference call re: Seresto Collar

Hi Bonnie,

As I suspected, study MRID 48240140 (Bayer ID 35992) requested below was the "compilation release rates in a series of studies" with the collars on cats and dogs. It was not a study unto itself. Attached is the DER.

Best regards,
Doug

Douglas A. Spilker, Ph.D.
Animal Health, EPA Regulatory Affairs

Science For A Better Life

Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201
USA

Tel: +1 913 268-2751
Mobile: +1 816 506-3102
E-mail: doug.spilker@bayer.com
Web: http://www.bayer.com

From: Adler, Bonnie [mailto:Adler.Bonnie@epa.gov]
Sent: Friday, April 22, 2016 10:11 AM
To: Bruce Martin; Doug Spilker
Subject: RE: Flumethrin conference call re: Seresto Collar

Bruce & Doug:

Here's a list of who was in attendance:

Bonnie Adler
Jill Bloom [PRD for my TL, Melanie Biscoe, who was not there]
Bo Davis – RD
Julie Breeden – RD
Wade Britten – HED
Monica Hawkins – HED
Julie VanAlstine – HED

The Human Health Risk Assessment can be found on Regulations.gov.
Look for EPA-HQ-OPP-2011-0013-0004 [not -0003 as stated on the call].

The data Wade mentioned, MRID 48240140 was a Release of ai to Cats & Dogs from 2010.
It was submitted but I have not yet found a review of it here. Wade is looking into that.

We will be interested in seeing the wipe/stroke [EU] data for the collar that you have.
And the narrative which explains the volatility and solubility of flumethrin.

Thanks again for participating in the call and for providing the information.
- Bonnie

From: Adler, Bonnie [mailto:Adler.Bonnie@epa.gov]
Sent: Friday, April 22, 2016 6:43 AM
To: Bruce Martin; Doug Spilker
Subject: RE: Flumethrin conference call next Friday with Wade & others re: Seresto Collar

Thanks Bruce.
I do need you to call into the conference line.
The information is here:
Ex. 6 PP - conference code/call in number

Thanks and we'll have several folks from HED & RD on the phone or in the conf room [lots of ppl telework on Fridays]
Thanks again for taking our call & questions. This step is crucial to ascertain the resultant residual.
Speak to you soon.
☺
Bonnie

From: Bruce Martin [mailto:bruce.martin@bayer.com]
Sent: Thursday, April 21, 2016 5:24 PM
To: Adler, Bonnie <Adler.Bonnie@epa.gov>; Doug Spilker <doug.spilker@bayer.com>
Cc: Bruce Martin <bruce.martin@bayer.com>
Subject: RE: Flumethrin conference call next Friday with Wade & others re: Seresto Collar

Bonnie,

Doug Spilker will not be available tomorrow. However, I will and will look forward to receiving the call-in information.

Best regards,

Bruce Martin
Director, Regulatory Affairs
Animal Health Development, North America

Science For A Better Life

Animal Health
Bayer HealthCare LLC
12809 Shawnee Mission Pkwy
Shawnee, KS 66216
USA

Tel: +1 913 268 2779
Fax: +1 913 268 2075
Mobile: +1 913 5235048
E-mail: bruce.martin@bayer.com
Web: http://www.bayer.com

From: Adler, Bonnie [mailto:Adler.Bonnie@epa.gov]
Sent: Friday, April 15, 2016 10:56 AM
To: Bruce Martin; Doug Spilker
Subject: RE: Flumethrin conference call next Friday with Wade & others re: Seresto Collar

Bruce,
Excellent, I'll set it up on my end.
With a call in number for you and a few others to use.
Thanks! I'm sorry I didn't do this the first time, but armed with that info, I hope the questions will be more pointed and we won't need too much of your time.
Have a nice weekend.
☺
Bonnie

From: Bruce Martin [mailto:bruce.martin@bayer.com]
Sent: Friday, April 15, 2016 11:45 AM
To: Adler, Bonnie <Adler.Bonnie@epa.gov>; Doug Spilker <doug.spilker@bayer.com>
Subject: RE: Flumethrin conference call next Friday with Wade & others re: Seresto Collar

Bonnie,
We can make ourselves available at that time next Friday.

Best regards,

Bruce Martin
Director, Regulatory Affairs
Animal Health Development, North America

Science For A Better Life

Animal Health
Bayer HealthCare LLC
12809 Shawnee Mission Pkwy
Shawnee, KS 66216
USA

Tel: +1 913 268 2779
Fax: +1 913 268 2075
Mobile: +1 913 5235048
E-mail: bruce.martin@bayer.com
Web: http://www.bayer.com

From: Adler, Bonnie [mailto:Adler.Bonnie@epa.gov]
Sent: Friday, April 15, 2016 10:23 AM
To: Doug Spilker
Cc: Bruce Martin
Subject: Flumethrin conference call next Friday with Wade & others re: Seresto Collar

Doug & Bruce,
Would you be available for a conference call with Wade [and others] next Friday 4/22 @10 am, EDT?
I want Wade to convey to you, personally, his needs for more information, data, etc and not have to talk thru me.

Let me know your availability. I would have done this sooner but he's out most of next week at an SAP meeting.
This was the only time I could grab him. I hope it works for others too.
Thanks,
Bonnie

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For alternate languages please go to http://bayerdisclaimer.bayerweb.com

Message

From: Biscoe, Melanie [Biscoe.Melanie@epa.gov]
Sent: 8/10/2016 2:59:57 PM
To: Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]; Adler, Bonnie [Adler.Bonnie@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]
CC: Evans, Elizabeth [Evans.Elizabeth@epa.gov]
Subject: RE: Conference Call with PMRA; Seresto

Adding Maria Piansay to this email, as flumethrin is transitioning from Bonnie to Maria.

Melanie Biscoe
Team Leader, Risk Management and Implementation Branch V
Pesticide Re-evaluation Division
Office of Pesticide Programs, US EPA
biscoe.melanie@epa.gov
703-305-7106

From: Rossmeisl, Colleen
Sent: Wednesday, August 10, 2016 10:15 AM
To: Davis, Kable <Davis.Kable@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Adler, Bonnie <Adler.Bonnie@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>
Cc: Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: Conference Call with PMRA; Seresto

Hi all -

I will likely be able to call in today for the meeting, but I am on leave with a couple of kids in the house, so not sure how much talking I will do!

My main questions for PMRA are re: Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Thanks!
Colleen

-----Original Appointment-----
From: Davis, Kable
Sent: Saturday, August 06, 2016 1:08 AM
To: Davis, Kable; Rossmeisl, Colleen; Echeverria, Marietta; Breeden-Alemi, Julie; Miller, David; Recore, Shanna; Adler, Bonnie; Biscoe, Melanie
Cc: Evans, Elizabeth

Subject: Conference Call with PMRA; Seresto
When: Wednesday, August 10, 2016 2:30 PM-3:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS7671C/Potomac-Yard-One

Exchange Server re-created a meeting that was missing from your calendar.

Sent by Microsoft Exchange Server

Message

From: Miller, David [Miller.DavidJ@epa.gov]
Sent: 6/9/2016 1:09:33 PM
To: Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]
CC: Sarkar, Bayazid [Sarkar.Bayazid@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]; Nguyen, James [Nguyen.James@epa.gov]; Evans, Elizabeth [Evans.Elizabeth@epa.gov]
Subject: RE: Bayer Slides
Attachments: Seresto slides for Bayer meeting 6-9-16 (002)_BS_6_8_16 sr_DJM2.pptx

Ok. Here are those edits.

From: Breeden-Alemi, Julie
Sent: Thursday, June 09, 2016 8:27 AM
To: Miller, David <Miller.DavidJ@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>
Cc: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Nguyen, James <Nguyen.James@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: RE: Bayer Slides

Good morning!

Marietta, Bo, and I just met and reviewed the slides for the meeting today with Bayer. One point that came was that it seems Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Many thanks, and please let us know if you have further discussion,
Julie

Julie A. Breeden-Alemi, DVM
U.S. Environmental Protection Agency
OCSPP / OPP / RD / IVB1
Breeden-Alemi.Julie@epa.gov
Phone: 703.347.0511
Office: S-7216, Mail Code: 7505P

From: Miller, David
Sent: Wednesday, June 08, 2016 4:05 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>
Cc: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Nguyen, James <Nguyen.James@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: Bayer Slides

Still finalizing these up, but here's the meat.

I'm here for a while if you want to talk. I will send around second draft later tonight for review tomorrow.

We probably want to add in a few slides regarding Ex. 5 Deliberative Process (DP) Shanna can add those in tomorrow am – she is at at 6 am.

David J. Miller CAPT | USPHS
Chief, Chemistry & Exposure Branch
and Acting Chief, Toxicology & Epidemiology Branch
Health Effects Division
Office of Pesticide Programs
703-305-5352 (voice)
703-305-5147 (fax)

Visit www.epa.gov/pesticides

Message

From: Adler, Bonnie [Adler.Bonnie@epa.gov]
Sent: 2/11/2016 6:34:51 PM
To: Arrington, Linda [Arrington.Linda@epa.gov]; Atwood, Donald [Atwood.Donald@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Britton, Wade [Britton.Wade@epa.gov]; Cook, Colwell [cook.colwell@epa.gov]; Craig, Evisabel [Craig.Evisabel@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; English, LisaRenee [English.LisaRenee@epa.gov]; Hanson, Charmaine [Hanson.Charmaine@epa.gov]; Hawkins, Monica [Hawkins.Monica@epa.gov]; Holmes, Jean [Holmes.Jean@epa.gov]; Jarboe, Stephen [Jarboe.Steve@epa.gov]; Jones, Arnet [Jones.Arnet@epa.gov]; Kaul, Monisha [Kaul.Monisha@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Prieto, Rafael [Prieto.Rafael@epa.gov]; Sims, Diann [Sims.Diann@epa.gov]; Suarez, Mark [Suarez.Mark@epa.gov]; VanAlstine, Julie [VanAlstine.Julie@epa.gov]; White, Katrina [White.Katrina@epa.gov]
CC: Steeger, Thomas [Steeger.Thomas@epa.gov]
Subject: Flumethrin Seresto briefing paper concerning incidents
Attachments: Seresto DD Briefing final draft.pptx

Team:
Thanks for a speedy meeting. I think we can agree that this one should not be all too hard, esp b/c it's new.

BEAD and EFED will check to see if they have deliverables, but I do agree that we have the information we need through RD and HED.

HED – Monica will be meeting with Wade Britton and Donna Davis next week and will let me know about the dates for their Scoping Document.

RD will keep us appraised regarding **Ex. 5 Deliberative Process (DP)**
Ex. 5 Deliberative Process (DP)

I'll be in touch as things evolve, esp any incident information.
Thanks again.
☺
Bonnie

Bo just sent the briefing RD had with HED for all. (thanks Bo!)
I attached it again below, anyway.

Seresto DD Briefing final draf...

Review of Seresto Pet Collar Incident Data

RD & HED/CEB/TEB

December 16, 2015

1

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- Seresto: pet collar (dog & cat) containing 4.5% flumethrin and 10.0% imidacloprid
    - Intended to provide 8 months of control for fleas and ticks
- Submitted on September 23, 2010 as part of a new AI; Non-Food; Indoor Use submission for flumethrin
    - Seresto (EPA Reg. No. 11556-155) is currently the only registered end-use product for flumethrin
- Registered on March 16, 2012
- Currently Pending Registration with PMRA

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Acute Toxicity Review

- DP 385538; dated February 1, 2012
- Based on slow release of active ingredients, waivers were granted for oral tox, dermal tox, inhalation tox and eye irritation
- Not a dermal sensitizer
- Category IV for primary dermal irritation

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Companion Animal Safety Review

- DP 385560, 396978; completed January 27, 2012
- Protocols were submitted and accepted prior to conducting studies
- A total of 8 companion animal safety studies were submitted
- Studies classified as acceptable; support the proposed use of Seresto on adult dogs and puppies 7 weeks of age and older, and adult cats and kittens 10 weeks of age and older

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Efficacy Review

- DP 385561, 385623, 393362; completed on March 14, 2012
- A total of 20 studies were submitted
- Claim supported: "For 8 month prevention and treatment of ticks, fleas on dogs and cats"

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Press Inquiry

- July 27, 2015: EPA received a press inquiry from WNBC NY
  - Is EPA aware of any incidents surrounding Seresto and are there any ongoing investigations?
- Agency Response:

"The Seresto Flea Collar, EPA Reg. No. 11556-155, contains the active ingredients flumethrin and imidacloprid. As with all pesticide products, the collar underwent extensive testing, including a companion animal safety study, before being registered to ensure that when used according to the directions and precautions on the product label it will not have unreasonable adverse effects on pets, people, non-target species and the environment.

Although pesticide products are thoroughly tested before being registered and marketed, some adverse reactions may occur. For that reason, each registrant is required under FIFRA 6(a)(2) to submit data to EPA about the adverse incidents reported to them. Bayer has submitted reports as required. EPA routinely reviews this incident information to determine if there are problems, especially if there are unexpected or high numbers of incidents associated with the use of any registered pesticide product. Many variables must be taken into consideration when making an assessment, including number of packages sold and health of the animal.

At this point, EPA is closely evaluating the reported incidents on Seresto to determine whether there is a causal relationship between this product and the incidents reported. If at any time, we determine that the collar presents unacceptable risks, we will take action to mitigate those risks or remove the product from the marketplace."

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Timeline of Important Events

- 7/27/15; press inquiry received
- 7/29/15; first call with Bayer
  - Objective of call was to ask if they are aware of a high number of reported incidents
- 7/30/15; second call with Bayer
  - Objective of call was to request submission of incident data
- 7/30/15; Bayer emails sample of enhanced reporting format
- 8/3/15; Bayer emails incident information that was originally submitted to PMRA and published information regarding "Weber Effect"

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- 8/5/15; Bayer emails sales information for Seresto
- 8/19/15; EPA emails suggested template for incident data submission
- 8/28/15; Bayer submits incident data using EPA suggest format
- 9/2/15; HED meets with RD to provide preliminary findings
- 10/8/15; EPA emails follow-up questions based from 8/28 submission
- 10/27/15; EPA emails asking why there was a big increase in incidents between Q2 and Q3
- 11/5/15; third call with Bayer
    - Objective of call was to explain the increase in incidents between Q2 and Q3

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Initial IDS Query

- Media inquiry prompted OPP review of pet incidents by product in Aggregate IDS
- HED reviewed Seresto collar incident data using 3 distinct methods:
  1. Incident counts reported to Aggregate IDS
  2. Reporting Odds Ratio (ROR)
  3. Incident Rate Ratio (IRR)
- Additionally, HED reviewed the most recent quarterly data for seasonal trends

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The query in the above was Jan 1, 2012- July 29 2015. This graph is included merely to illustrate why OPP got worried about Seresto

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Method 1. IDS Aggregate Query Results

from 1/1/12 – 7/29/15

- In terms of incident counts Seresto ranked #1 by a wide margin, for (total) incident counts in IDS

Registration Number	Death	Major	Moderate	Unknown Effect	Low	No Effect	Total
011556-00155	212	707	2604	**0**	**6837**	**0**	**10360**
065331-00005	149	200	0	6199	0	0	6548
065331-00004	103	71	0	2920	0	0	3094

→ *Seresto*

Limitations:

- Pet incident reports are counts by severity- species unknown
- No descriptive detail available

Top three products
Seresto
Frontline plus for dogs
Frontline plus for cats

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Method 2. Reporting Odds Ratio

- Reporting Odds Ratio (ROR) calculated for all pet Spot On products with ten or more deaths reported in IDS
- ROR measures the odds of fatal or high severity incidents for Seresto compared to the odds of fatal or high severity incidents for all other products
- Calculation:
    1. X = death + major incident reports for Product A / all other (less severe) incident reports for Product A
    2. Y = death + major incident reports for all other (not Product A) products / all other (not Product A) less severe incident reports
    3. ROR = X/Y

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Reporting Odds Ratio

Benefits and Limitations

- **Does not require sales data**
- Incident data – issues with using counts:
  - Pet product labeling is inconsistent
    - Seresto = 1 registration # for all species/sizes combined
    - Other products have multiple registration #s by species, animal size
  - Hence, IDS reports, which are organized by product registration #, do not reflect these important distinctions

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combined the following:

· Advantage II for cats (11556-150 – kitten, 1156-151 – small cat, 11556-152 – large cat), · Advantage II for dogs (11556-128 – small dog, 11556-125 – medium dog, 11556-127 - large dog, and 11556-130 – extra-large dog)· K9 Advantix II (11556-132 –small dog, 11556-133 medium dog, 11556-134 extra-large dog, 11556-135 large dog)

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Reporting Odds Ratio

- ROR Results for Death + Major

EPA Reg. No.	Product Name	known cases	Deaths	Majors	OR	CI
011556-00155	Seresto	9526	190	627	1.23	1.14, 1.34
011556-00144	K9 Advantix Plus 100	3117	101	186	1.30	1.15, 1.48
065331-00005	Frontline plus for dogs	3959	93	117	0.69	0.60, 0.80

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We calculated ROR for all pet products with 10 or more deaths- this table is the top three products in terms of pet deaths + major
IDS data from 2013/2014 was originally used ***These ROR have been updated with more recent data***
K9 product only includes large dog
Frontline for dogs

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Reporting Odds Ratio

- ROR Results for Deaths Only:

EPA Reg. No.	Product Name	known cases	Deaths	OR	CI
011556-00155	Seresto	9526	190	0.74	0.63, 0.86
011556-00144	K9 Advantix Plus 100	3117	101	1.30	1.05, 1.59
065331-00005	Frontline plus for dogs	3959	93	0.91	0.73, 1.12

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IDS data from 2013/2014 was originally used ***These ROR have been updated with more recent data***
K9 product only includes large dog
Frontline for dogs

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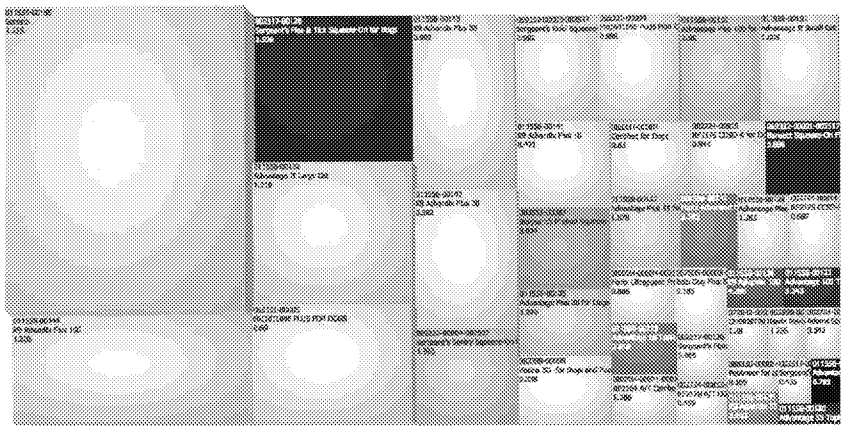
ROR Tree Diagram

data signals



Indicator of disproportionality
Size = death+major counts /
Color is a gradation of ROR – lightest to darkest with black being highest OR

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ROR Tree Diagram

data signals

Multivariate tree diagram – check for signals
Seresto- 817= deaths + majors
GREEN BOXES DO NOT DIFFER FROM THE AVERAGE RISK
Each box represents # of death+ majors, the height represents the deaths, and color represents the Reporting Odds Ratio

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Method 3. Incident Rate Ratio (IRR)

- Seresto and other Bayer product sales data was obtained
- This allowed HED to:
  - Calculate the Incident Rate Ratio
    - a standard method of comparing incident rates
    - Control for 8 months Seresto vs. 1 month Spot-On
      - IR_A = incident counts for Product A/ "pet-months" for Product A
      - IR_B = incident counts for Product B/ "pet-months" for Product B
      - IRR = IR_A / IR_B
- Used the Poisson Regression Model
  - Allows one to obtain confidence limits around IRR
  - Can determine statistically significant differences between products

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Seresto last 8 months = 8,000 pet months of exposure whereas Spot-ons = 1,000 pet months of exposure

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Ex. 4 CBI

Outcome Death
Seresto vs. Frontline – 2014

Ex. 4 CBI

Need to consider limitations in data- reporting high severity cases for symptoms lasting 60 days or more whereas other registrants may classify rash etc as moderate –

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Incident Rate Ratio

Benefits:

- The most valid method of analysis
- Sales data utilized

Limitations:

- Data inconsistencies
  - Seresto has one registration number for all collars
  - Sales data was approximated
    - Availability of sales information varied among products
  - Use of 2013/2014 data & the Weber Effect

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Recent Seresto Data Submission

- Third quarter 2015 Bayer incident data was received in October 2015.
- OPP noted a jump in major severity incidents for Q3
- HED compared Seresto and three other Bayer pet products using incident counts for the 6 most recent quarters of data
- Based on newest available incident data
- Looking for a similar jump in incidents among other pet products that would indicate a seasonal trend

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In Mid-October , When Bayer submitted the 3rd quarter Seresto incidents there was an increase in deaths and majors. We compared the same 6 quarter for 4 bayer products to see if other products followed this trend or if it was just Seresto.

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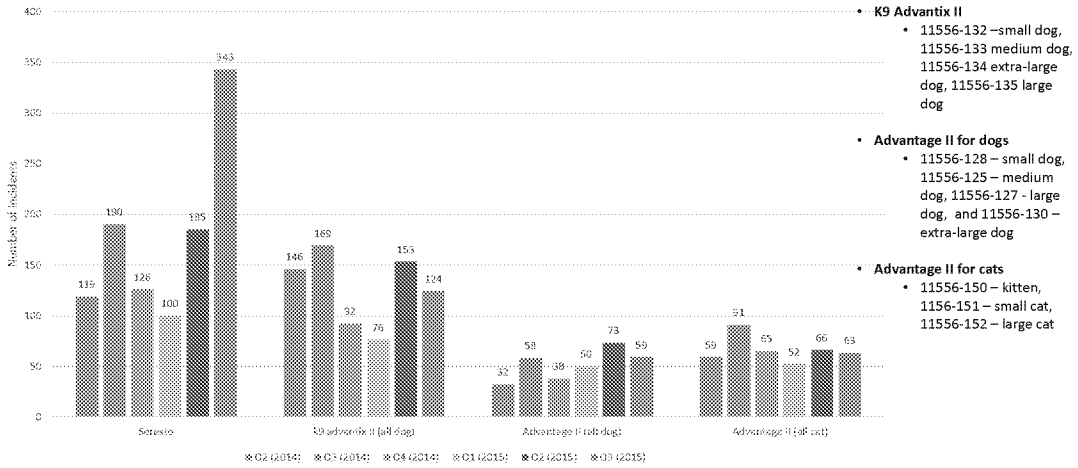
Figure 1. Bayer **Death and Major** Domestic Animal Incidents Reported to Aggregate IDS for 2014 Q2,Q3,Q4 and 2015 Q1,Q2,Q3



21

Ex. 5 Deliberative Process (DP)

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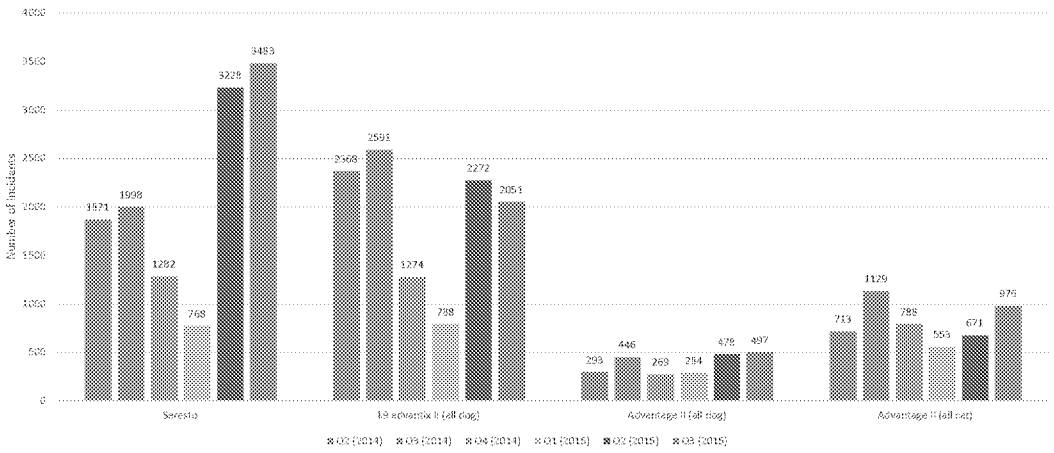
Figure 2. Bayer Domestic Animal **Total Incidents** Reported to Aggregate IDS for 2014 Q2,Q3,Q4 and 2015 Q1,Q2,Q3



22

Ex. 5 Deliberative Process (DP)

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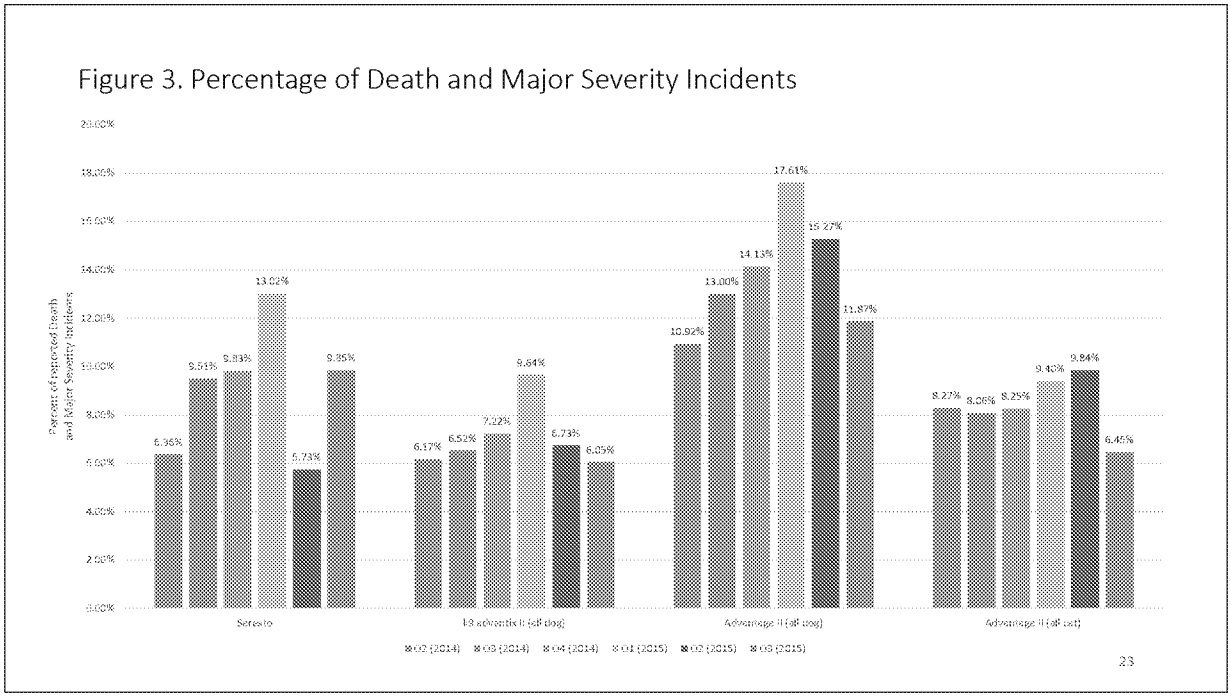

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Call with Bayer on 2015 Q3 incident data

- EPA- Why the jump in FY 15 Q3 major incidents?

Bayer Response:

- Record collar sales in FY 15 Q2
  - Q3 incidents likely reflective of Q2 sales
  - Sales 126% above that of the previous quarter
  - This quarter was more than all 2014 Seresto sales combined
- Bayer is conservative with high severity coding; 60% are moderate
  - >60 days dermal rash is classified as DB (major severity)
  - Unclear how other registrants are coding

EPA Next Steps: continue to monitor this situation

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DA – Death – if the domestic animal died or was euthanized;
DB – Major – if the domestic animal exhibited or was alleged to have exhibited symptoms which may have been life-threatening or resulted in residual disability;
DC – Moderate – if the domestic animal exhibited or was alleged to have exhibited symptoms which are more pronounced, more prolonged or of a more systemic nature than minor symptoms and included some treatment and return to pre-exposure state;
DD – Minor – if the domestic animal was alleged to have exhibited symptoms, but they were minimally bothersome and resolved rapidly;
DE – Unknown – if symptoms are unknown or not specified.

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Limitations with Pet Product Incident Data

Potential confounders described by Bayer:

- Variability between companies
  - Bayer has a 24 hour reporting hotline
  - Differences among registrants regarding severity classification
- Variability between products
  - Weber effect
  - Seeing the collar each days serves to visually remind pet owners of the exposure
  - Seresto has one registration # for all species/sizes whereas other products tend to have a separate registration #'s for the species/sizes

25

Advantage II for cats (11556-150 – kitten, 1156-151 – small cat, 11556-152 – large cat), Advantage II for dogs (11556-128 – small dog, 11556-125 – medium dog, 11556-127 - large dog, and 11556-130 – extra-large dog)K9 Advantix II (11556-132 –small dog, 11556-133 medium dog, 11556-134 extra-large dog, 11556-135 large dog)

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PMRA Collaboration

- PMRA contacted EPA requesting incident information on Seresto
  - Bayer submitted a registration for the product in Canada
- PMRA has a standard method of review for pet incidents
  - Plausibility document
    - The draft is currently under review at EPA
    - Plausibility document is a guide for looking at toxicology profile together with incident symptoms reported for consistency
  - Causality analysis currently being conducted
    - EPA will conduct a peer review of the results of the causality analysis
    - Expect causality analysis delivery to EPA for review in mid-February
- HED ensure use of standardized VedDRA terminology for the PMRA case by case review
  - e.g. seizure versus convulsion
  - Link to VedDRA symptom terminology: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017752.xls

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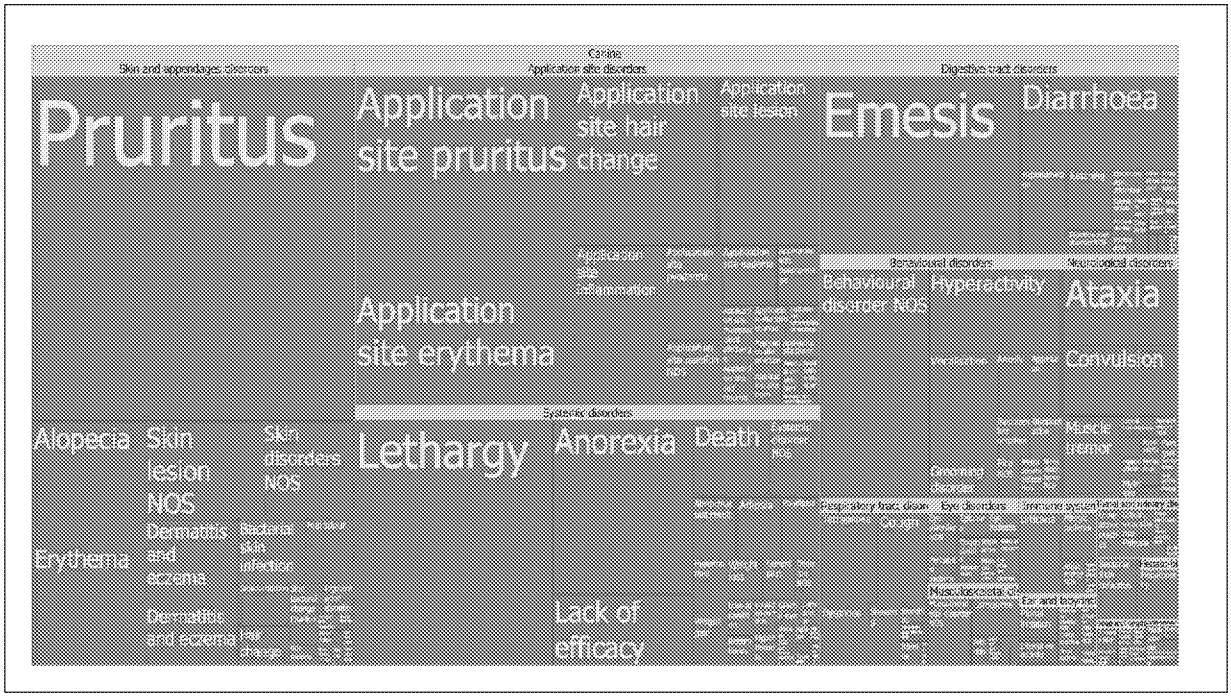

Vedra dictionary
Based upon Bayer submission on Seresto 2012-July 2015 – includes all Seresto incidents since registration

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Next Steps

- Await PMRA Causality Analysis for Seresto collars for EPA peer review
- Update the ROR analysis with the most current Seresto incident data
  - 2014-2015 data will replace 2013-2014 data
- IRR may be updated when all data elements and sales information for 2015 become available
- Communicate with PMRA on Seresto decisions in February/March 2016

Benefits:
Seresto is no longer brand new (Weber effect non-issue)

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What have we learned?

Ex. 5 Deliberative Process (DP)

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Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 2/11/2016 6:29:55 PM
To: Adler, Bonnie [Adler.Bonnie@epa.gov]; Hawkins, Monica [Hawkins.Monica@epa.gov]; VanAlstine, Julie [VanAlstine.Julie@epa.gov]; Craig, Evisabel [Craig.Evisabel@epa.gov]; English, LisaRenee [English.LisaRenee@epa.gov]; Cook, Colwell [cook.colwell@epa.gov]; Atwood, Donald [Atwood.Donald@epa.gov]; Britton, Wade [Britton.Wade@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Hanson, Charmaine [Hanson.Charmaine@epa.gov]; Jarboe, Stephen [Jarboe.Steve@epa.gov]; Jones, Arnet [Jones.Arnet@epa.gov]; Kaul, Monisha [Kaul.Monisha@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Prieto, Rafael [Prieto.Rafael@epa.gov]; Sims, Diann [Sims.Diann@epa.gov]; Suarez, Mark [Suarez.Mark@epa.gov]; Holmes, Jean [Holmes.Jean@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; White, Katrina [White.Katrina@epa.gov]
CC: Steeger, Thomas [Steeger.Thomas@epa.gov]
Subject: RE: Flumethrin First Team Meeting
Attachments: Seresto DD Briefing final draft.pptx

Everyone –

Here are the slides from our 12/16/15 DD briefing.

Seresto DD Briefing final draf...

-----Original Appointment-----
From: Adler, Bonnie
Sent: Monday, December 21, 2015 1:38 PM
To: Adler, Bonnie; Hawkins, Monica; VanAlstine, Julie; Craig, Evisabel; English, LisaRenee; Cook, Colwell; Atwood, Donald; Britton, Wade; Echeverria, Marietta; Hanson, Charmaine; Jarboe, Stephen; Jones, Arnet; Kaul, Monisha; Kiely, Timothy; Prieto, Rafael; Sims, Diann; Suarez, Mark; Holmes, Jean; Arrington, Linda; Biscoe, Melanie; Davis, Donna; Davis, Kable; White, Katrina
Cc: Steeger, Thomas
Subject: Flumethrin First Team Meeting
When: Thursday, February 11, 2016 1:00 PM-2:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS9100/Potomac-Yard-One

Hi folks.
I have attached the Agenda and added more members to this list.
☺
<< File: Draft Agenda Flumehtrin First Team meeting 2-11-16.docx >>
Although Flumethrin is part of the 'Pyrethrins' work group, it may be excluded as it's use is limited to pet collars. [for now]

Thanks!
Bonnie

Message

From: Miller, David [Miller.DavidJ@epa.gov]
Sent: 2/8/2016 1:58:30 PM
To: Evans, Elizabeth [Evans.Elizabeth@epa.gov]; Nguyen, James [Nguyen.James@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]; Sarkar, Bayazid [Sarkar.Bayazid@epa.gov]
CC: Davis, Kable [Davis.Kable@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: FW: Question on pet incidents relating to Seresto flea and tick collar
Attachments: Ask EMA - (ASK-17662) Question on pet incidents relating to Seresto flea and tick collar

See below and attached re: the EMA response to my query. It looks like the Germans will be the folks we need to contact for this.

Their initial response got labeled as spam.

David.

From: Schalansky Jana [mailto:Jana.Schalansky@ema.europa.eu]
Sent: Monday, February 08, 2016 8:48 AM
To: Miller, David <Miller.DavidJ@epa.gov>
Subject: FW: Question on pet incidents relating to Seresto flea and tick collar

Dear Mr Miller,

Please see attached the response sent last Thursday, which may have been blocked by your spam filter.

Please let me know if you require any further information.

Kind regards,

Jana Schalansky
Business Programme Manager
Head of Division Support
Veterinary Medicines Division

European Medicines Agency
30 Churchill Place | Canary Wharf | London E14 5EU | United Kingdom
Tel. +44 (0)20 3660 8542 | Fax +44 (0)20 3660 5545
jana.schalansky@ema.europa.eu | www.ema.europa.eu

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From: Miller, David [mailto:Miller.DavidJ@epa.gov]
Sent: 08 February 2016 12:59
To: Vet PhV
Subject: FW: Question on pet incidents relating to Seresto flea and tick collar

Dear Dr. Olaerts,

I am just following up on my previous email. Is there any data or reports you might have that might have or that you could direct us to that might help us in our pharmaco-vigilance review of Bayer's Seresto collar?

Thank you.

David.

From: Miller, David
Sent: Wednesday, February 03, 2016 10:10 AM
To: 'vet-phv@ema.europa.eu' <vet-phv@ema.europa.eu>
Subject: Question on pet incidents relating to Seresto flea and tick collar

Dear Dr. Olaerts,

My name is David Miller and I am a branch chief in the US Environmental Protection Agency's Office of Pesticide Programs of a branch which deals with toxicovigilance issues associated with pet products. We are working closely the Canada's Pest Management Regulatory Agency which is working to determine whether to approve the registration of Bayer Animal Health's Seresto flea and tick collar for dogs and cats (U.S. EPA Registration Number 11556-155) containing the active ingredients flumethrin and imidacloprid. One aspect of this work is the investigation of reported incidents potentially associated with these collars.

We understand that you are listed as EMA's contact for medicinal products for veterinary use and the EMA recently approved the collar to move from veterinary prescription (only) to over-the-counter sales. I wondered if you had any information or reports on incidents that may be associated with this product that you might be willing to make available to us or any reports or analyses that you may have done to approve the re-designation of this product to an over-the-counter sales use.

Thank you for any assistance you may be able to provide.

Regards,

David.

David J. Miller CAPT | USPHS
Chief, Chemistry & Exposure Branch
and Acting Chief, Toxicology & Epidemiology Branch
Health Effects Division
Office of Pesticide Programs
703-305-5352 (voice)
703-305-5147 (fax)

Visit www.epa.gov/pesticides

This e-mail has been scanned for all known viruses by European Medicines Agency.

Message

From: askema-no_reply [askema-no_reply@ema.europa.eu]
Sent: 2/4/2016 3:46:00 PM
To: Miller, David [Miller.DavidJ@epa.gov]
CC: Schalansky Jana [Jana.Schalansky@ema.europa.eu]
Subject: Ask EMA - (ASK-17662) Question on pet incidents relating to Seresto flea and tick collar

Re: EMA request reference ASK-17662

Dear Mr Miller,

your query was forwarded to me for response.

Please note that the Seresto flea and tick collar was not authorised by the EMA, which would mean central authorisation in all EU member states. Instead, it had been authorised nationally in Germany, and was later extended to other Member States via the so-called mutual recognition procedure. You can find those details in the Veterinary Mutual Recognition Index (VMRI): http://mri.medagencies.org/Veterinary/Product/Details/85.

Therefore, any change from prescription to OTC status was also handled by the German authorities, not the European Medicines Agency, and we do not hold any information on it. We would advise that you contact the German competent authority directly, which would be the Federal Office of Consumer Protection and Food Safety (contact details are available on the HMA website: http://www.hma.eu/nationalcontacts_vet.html?showctr=1).

I hope this information is helpful.

Kind regards,

Jana Schalansky

European Medicines Agency
30 Churchill Place | Canary Wharf | London E14 5EU | United Kingdom

Got a question? Ask EMA at www.ema.europa.eu/contact

This message and any attachment contain information which may be confidential or otherwise protected from disclosure. It is intended for the addressee(s) only and should not be relied upon as legal advice unless it is otherwise stated. If you are not the intended recipient(s) (or authorised by an addressee who received this message), access to this e-mail, or any disclosure or copying of its contents, or any action taken (or not taken) in reliance on it is unauthorised and may be unlawful. If you have received this e-mail in error, please inform the sender immediately.

Original request: Question on pet incidents relating to Seresto flea and tick collar

From: Miller, David [mailto:Miller.DavidJ@epa.gov] Sent: 03 February 2016 15:10 To: Vet PhV Subject: Question on pet incidents relating to Seresto flea and tick collar Dear Dr. Olaerts, My name is David Miller and I am a branch chief in the US Environmental Protection Agency's Office of Pesticide Programs of a branch which deals with toxicovigilance issues associated with pet products. We are working closely the

Canada's Pest Management Regulatory Agency who is working to determine to approve the registration of Bayer Animal Health's Seresto flea and tick collar for dogs and cats (U.S. EPA Registration Number 11556-155) containing the active ingredient flumethrin and imidacloprid. One aspect of this work is the investigation of reported incidents potentially associated with these collars. We understand that you are listed as EMA's contact for medicinal products for veterinary use and the EMA recently approved the collar to move from veterinary prescription (only) to over-the-counter sales. I wondered if you had any information or reports on incidents that may be associated with this product that you might be willing to make available to us or any reports or analyses that you may have done to approve the re-designation of this product to an over-the-counter sales. Thank you for any assistance you may be able to provide. Regards, David. _____ David J. Miller CAPT | USPHS Chief, Chemistry & Exposure Branch and Acting Chief, Toxicology & Epidemiology Branch Health Effects Division Office of Pesticide Programs 703-305-5352 (voice) 703-305-5147 (fax) Visit www.epa.gov/pesticides

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 4/27/2016 11:27:53 AM
To: Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Breeden, Julie [Breeden.Julie@epa.gov]
Subject: FW: Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Stroke Study Cat
Attachments: 35121ene.pdf

FYI

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Tuesday, April 26, 2016 5:03 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Adler, Bonnie <Adler.Bonnie@epa.gov>
Subject: Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Stroke Study Cat

Dear Mr. Davis,

As requested by the Agency in the teleconference of April 22, 2016, please find attached unofficial copies of the "Seresto Stroke studies" on cats.

The official copies are being submitted to the Agency by FedEx for official processing via Document Processing Desk.

Best regards,
Doug

Douglas A. Spilker, Ph.D.
Animal Health, EPA Regulatory Affairs

Science For A Better Life

Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201
USA

Tel: +1 913 268-2751
Mobile: +1 816 506-3102
E-mail: doug.spilker@bayer.com
Web: http://www.bayer.com

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Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 4/27/2016 11:26:47 AM
To: Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Breeden, Julie [Breeden.Julie@epa.gov]
Subject: FW: Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Stroke Study Dog
Attachments: 35120ene.pdf; Davis PNR 1427 4-26-2016.pdf

FYI

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Tuesday, April 26, 2016 5:03 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Adler, Bonnie <Adler.Bonnie@epa.gov>
Subject: Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Stroke Study Dog

Dear Mr. Davis,

As requested by the Agency in the teleconference of April 22, 2016, please find attached our cover letter and unofficial copies of the "Seresto Stroke studies" on dogs.

The official copies are being submitted to the Agency by FedEx for official processing via Document Processing Desk.

Best regards,
Doug

Douglas A. Spilker, Ph.D.
Animal Health, EPA Regulatory Affairs

Science For A Better Life

Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201
USA

Tel: +1 913 268-2751
Mobile: +1 816 506-3102
E-mail: doug.spilker@bayer.com
Web: http://www.bayer.com

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Message

From: Biscoe, Melanie [Biscoe.Melanie@epa.gov]
Sent: 4/27/2016 3:37:49 PM
To: Adler, Bonnie [Adler.Bonnie@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Atwood, Donald [Atwood.Donald@epa.gov]; Britton, Wade [Britton.Wade@epa.gov]; Cook, Colwell [cook.colwell@epa.gov]; Craig, Evisabel [Craig.Evisabel@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; English, LisaRenee [English.LisaRenee@epa.gov]; Hanson, Charmaine [Hanson.Charmaine@epa.gov]; Hawkins, Monica [Hawkins.Monica@epa.gov]; Holmes, Jean [Holmes.Jean@epa.gov]; VanAlstine, Julie [VanAlstine.Julie@epa.gov]; White, Katrina [White.Katrina@epa.gov]
CC: Bloom, Jill [Bloom.Jill@epa.gov]
Subject: RE: FYI - Flumethrin/Seresto incident meeting with FDA

I'm also confused as to why PRD wasn't invited to this meeting.

In any case, we look forward to hearing more updates on this from the team on how the incidents are being/will be considered leading up to cross-OPP risk management decisions.

Melanie Biscoe
Team Leader, Risk Management and Implementation Branch V
Pesticide Re-evaluation Division
Office of Pesticide Programs, US EPA
biscoe.melanie@epa.gov
703-305-7106

From: Adler, Bonnie
Sent: Wednesday, April 27, 2016 11:24 AM
To: Arrington, Linda <Arrington.Linda@epa.gov>; Atwood, Donald <Atwood.Donald@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Britton, Wade <Britton.Wade@epa.gov>; Cook, Colwell <cook.colwell@epa.gov>; Craig, Evisabel <Craig.Evisabel@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; English, LisaRenee <English.LisaRenee@epa.gov>; Hanson, Charmaine <Hanson.Charmaine@epa.gov>; Hawkins, Monica <Hawkins.Monica@epa.gov>; Holmes, Jean <Holmes.Jean@epa.gov>; VanAlstine, Julie <VanAlstine.Julie@epa.gov>; White, Katrina <White.Katrina@epa.gov>
Cc: Bloom, Jill <Bloom.Jill@epa.gov>
Subject: FYI - Flumethrin/Seresto incident meeting with FDA

I saw this in the weekly, but I was unaware of it until I saw this item.
We need to be sure we're tapped into the information across OPP.

Also, Doug sent Bo the information we were seeking from our Conf call with Bayer last Friday.
I have copies of the Cat & Dog Stroke studies.
I'll share those in a different email.

Please share if you see or hear something about Seresto/Flumethrin.
We need to try to keep ahead/abreast of the issues surrounding on this case.
☺
Bonnie

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 7/5/2016 4:48:16 PM
To: Doug Spilker [doug.spilker@bayer.com]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: RE: Seresto - Proposed Studies for Discussion with PMRA

Perfect. Thanks, Doug!

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Tuesday, July 05, 2016 12:45 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: RE: Seresto - Proposed Studies for Discussion with PMRA

Bo, Still awaiting confirmation of the meeting date with PMRA (next week proposed.) Have to talk with them first. As soon as there is a draft to send, I will get it to you. Thanks for the offer.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

From: Davis, Kable [mailto:Davis.Kable@epa.gov]
Sent: Tuesday, July 05, 2016 11:43 AM
To: Doug Spilker
Cc: Echeverria, Marietta; Bruce Martin
Subject: RE: Seresto - Proposed Studies for Discussion with PMRA

Doug –

Thanks for sending the bullets. Any idea when the protocol for the short-term animal safety study should be submitted? You may want to forward me a courtesy copy when you submit, so I can pass that along for initial review. It may speed things up on our end.

Thanks,
Bo

Kable Bo Davis

Product Manager 3
Invertebrate & Vertebrate Branch 1
(703) 306-0415
davis.kable@epa.gov

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Tuesday, July 05, 2016 12:37 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Bruce Martin <bruce.martin@bayer.com>
Subject: Seresto - Proposed Studies for Discussion with PMRA

Dear Mr. Kable,

As discussed in the teleconference between Bayer Animal Health and EPA on June 30th, Bayer will be proposing additional studies that should provide data to assist PMRA in refining their draft evaluations. The proposed studies that will be discussed with PMRA in the next few weeks include:

1. Dermal penetration study(ies) with flumethrin
2. Hand-to-mouth exposure assessment following dog stroking
3. Short-term animal safety study with a pharmacokinetic component evaluating earlier blood concentrations of the active ingredients, where previous studies did not demonstrate blood concentrations at less than 7 days post-collar application.
4. Pharmacokinetic studies in rodents at doses, especially NOEL, used in the laboratory oral tox studies.

   The goal of studies #3 and 4 will be to compare systemic exposure in dogs following collar application compared to systemic exposure in the laboratory oral tox studies. That is, does the systemic exposure following collar application justify the plausibility assessment?

After agreement in principle regarding the studies that PMRA would find useful to refine their assessments of Seresto, we will present this information to EPA, as well. Any protocols sent to PMRA for review, will also be sent concurrently to EPA for timely review. Because PMRA wants the additional studies to begin as soon as possible, the protocol reviews (and amendment cycles, if needed) must be completed as soon as possible.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 5/27/2016 10:48:05 AM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: RE: Seresto thoughts

No, however I'll do some digging and will find out.

-----Original Message-----
From: Echeverria, Marietta
Sent: Friday, May 27, 2016 6:46 AM
To: Davis, Kable <Davis.Kable@epa.gov>
Subject: Seresto thoughts

It would seem Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)

I want to talk to PMRA next week before the bayer meeting. Do you know who my counterpart is in the registration directorate?

Sent from my iPhone

Message

From: Adler, Bonnie [Adler.Bonnie@epa.gov]
Sent: 4/27/2016 3:37:30 PM
To: Arrington, Linda [Arrington.Linda@epa.gov]; Atwood, Donald [Atwood.Donald@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Britton, Wade [Britton.Wade@epa.gov]; Cook, Colwell [cook.colwell@epa.gov]; Craig, Evisabel [Craig.Evisabel@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; English, LisaRenee [English.LisaRenee@epa.gov]; Hanson, Charmaine [Hanson.Charmaine@epa.gov]; Hawkins, Monica [Hawkins.Monica@epa.gov]; Holmes, Jean [Holmes.Jean@epa.gov]; VanAlstine, Julie [VanAlstine.Julie@epa.gov]; White, Katrina [White.Katrina@epa.gov]
CC: Bloom, Jill [Bloom.Jill@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]
Subject: --> Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Formulation and Release Information
Attachments: 44259ene.pdf; Davis PNR 1427 Release Info 4-26-2016.pdf; Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Stroke Study Dog; Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Formulation and Release Information

Team,
This document is the narrative from Bayer from last week's conference call.
It explains the manufacturing process and details of how the collar is supposed to work.

I have also attached the emails that contain the Stroke Study on Cats and the Stroke Study on Dogs that was mentioned.
MRIDs will be shared later when they are assigned.

In addition, I included David Miller on this note if only to be inclusive to share this information for our Flumethrin discussions.
Thanks,
Bonnie

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Tuesday, April 26, 2016 4:45 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Adler, Bonnie <Adler.Bonnie@epa.gov>; Bruce Martin <bruce.martin@bayer.com>
Subject: Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Formulation and Release Information

Dear Mr. Davis,

As requested by the Agency in the teleconference of April 22, 2016, please find attached our cover letter and an unofficial copy of the "Seresto release and formulation information."

The official copies are being submitted to the Agency by FedEx for official processing via Document Processing Desk.

Best regards,
Doug

Douglas A. Spilker, Ph.D.
Animal Health, EPA Regulatory Affairs

Science For A Better Life

Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201
USA

Tel: +1 913 268-2751
Mobile: +1 816 506-3102
E-mail: doug.spilker@bayer.com
Web: http://www.bayer.com

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Message

From: Doug Spilker [doug.spilker@bayer.com]
Sent: 4/26/2016 9:02:31 PM
To: Davis, Kable [Davis.Kable@epa.gov]
CC: Adler, Bonnie [Adler.Bonnie@epa.gov]
Subject: Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Stroke Study Dog
Attachments: 35120ene.pdf; Davis PNR 1427 4-26-2016.pdf

Flag: Follow up

Dear Mr. Davis,

As requested by the Agency in the teleconference of April 22, 2016, please find attached our cover letter and unofficial copies of the "Seresto Stroke studies" on dogs.

The official copies are being submitted to the Agency by FedEx for official processing via Document Processing Desk.

Best regards,
Doug

Douglas A. Spilker, Ph.D.
Animal Health, EPA Regulatory Affairs

Science For A Better Life

Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201
USA

Tel: +1 913 268-2751
Mobile: +1 816 506-3102
E-mail: doug.spilker@bayer.com
Web: http://www.bayer.com

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Message

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 4/26/2016 8:49:28 PM
To: Miller, David [Miller.DavidJ@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Breeden, Julie [Breeden.Julie@epa.gov]
Subject: FW: Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Formulation and Release Information
Attachments: 44259ene.pdf; Davis PNR 1427 Release Info 4-26-2016.pdf

Everyone –

Here is Bayer's wipe study, which is being submitted formally through the front-end. PRD wanted to see it as well.

Let me know if you have any questions.
Bo

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Tuesday, April 26, 2016 4:45 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Adler, Bonnie <Adler.Bonnie@epa.gov>; Bruce Martin <bruce.martin@bayer.com>
Subject: Seresto (PNR 1427 Insecticide; EPA Reg. 11556-155) - Formulation and Release Information

Dear Mr. Davis,

As requested by the Agency in the teleconference of April 22, 2016, please find attached our cover letter and an unofficial copy of the "Seresto release and formulation information."

The official copies are being submitted to the Agency by FedEx for official processing via Document Processing Desk.

Best regards,
Doug

Douglas A. Spilker, Ph.D.
Animal Health, EPA Regulatory Affairs

Science For A Better Life

Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201
USA

Tel: +1 913 268-2751
Mobile: +1 816 506-3102
E-mail: doug.spilker@bayer.com
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Message

From: Isbell, Diane [Isbell.Diane@epa.gov]
Sent: 6/29/2016 2:44:15 PM
To: Lewis, Susan [Lewis.Susan@epa.gov]
CC: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: RE: review of flumethrin/imidicloprid pet collar

Sure.

From: Lewis, Susan
Sent: Wednesday, June 29, 2016 10:43 AM
To: Isbell, Diane <Isbell.Diane@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: RE: review of flumethrin/imidicloprid pet collar

Can you ask for another time.

Susan Lewis
Director, Registration Division
Office of Pesticide Program
U.S.E.P.A
703-308-8009

From: Isbell, Diane
Sent: Wednesday, June 29, 2016 10:35 AM
To: Lewis, Susan <Lewis.Susan@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: FW: review of flumethrin/imidicloprid pet collar

Hi Susan,
For the conference call with PMRA on the flumethrin/imidicloprid pet collar, they proposed July 13th from 3 – 4 or the 15th. However, it looks like you are off on the 15th. You have a conflict during that time with the Resource Meeting with Delores Barber. Is it ok to schedule it during this time? If not, I can go back to PMRA and ask for additional times. Thanks, Diane

---

From: Echeverria, Marietta
Sent: Wednesday, June 29, 2016 10:23 AM
To: Isbell, Diane <Isbell.Diane@epa.gov>
Subject: RE: review of flumethrin/imidicloprid pet collar

Focus the calendar based on Susan and my availability, but also invite Bo, Dave Miller and Donna Davis. Thank you

---

From: Isbell, Diane
Sent: Wednesday, June 29, 2016 10:18 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: FW: review of flumethrin/imidicloprid pet collar

Is the meeting with Susan and you. Is there anyone else? It sounds like they're inviting HED.

From: Squires, Janice (HC/SC) [mailto:janice.squires@canada.ca]
Sent: Wednesday, June 29, 2016 10:10 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Isbell, Diane <Isbell.Diane@epa.gov>; Sterkenburg, Neilda (HC/SC) <neilda.sterkenburg@canada.ca>
Subject: RE: review of flumethrin/imidicloprid pet collar

Hi Marietta,

Please let me know if you would be available:

July 13th, 3-4 p.m.
July 15th, anytime between 9:00-12 and 1:00-4:00

Thank you,
Janice

From: Echeverria, Marietta [mailto:Echeverria.Marietta@epa.gov]
Sent: 2016-06-28 2:12 PM
To: Sterkenburg, Neilda (HC/SC)
Cc: Isbell, Diane; Squires, Janice (HC/SC)
Subject: RE: review of flumethrin/imidicloprid pet collar

Hi Neilda,

Thank you for the update and I certainly understand the need to consult with counsel. We'll look for the email with possible dates for a phone call and go from there.

Cheers,
Marietta

From: Sterkenburg, Neilda (HC/SC) [mailto:neilda.sterkenburg@canada.ca]
Sent: Tuesday, June 28, 2016 12:06 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Isbell, Diane <Isbell.Diane@epa.gov>; Squires, Janice (HC/SC) <janice.squires@canada.ca>
Subject: RE: review of flumethrin/imidicloprid pet collar

Hi Marietta,

Sorry for not having replied to your email, I've had to consult our legal service with respect to what we can, and cannot, chat about on this file. We've shared the outcome of our reviews with Bayer CropScience, and they have asked explicitly that we not share our reviews with regulatory partners, thus the need for me to consult with legal.

I think a phone call is a good idea. I'm assuming that you would like Peter Chan on the call, however he'll be away for the month of July. Having said that, we'll arrange for either Yad Bhuller or Connie Moase to participate in the call. Also, it would be a good idea for Peter Brander (our Chief Registrar) to participate. I'll ask my assistant to come up with a few possible days and times asap and we'll be in touch.

Again, my apologies for not having replied, I just had to wait to chat with legal, which I just did late yesterday. Thanks for your understanding.

Regard,

Neilda

Neilda Sterkenburg
Director | Directrice
Review and Science Integration Division | Division des examens et de l'intégration scientifique
Pest Management Regulatory Agency | Agence règlementaire de la lutte antiparasitaire
Health Canada | Santé Canada
Suite E602, 2720 Riverside Drive,
Ottawa, ON Canada K1A OK9
neilda.sterkenburg@canada.ca
Telephone | Téléphone: 613-736-3851
Government of Canada | Gouvernement du Canada

Health Canada Santé Canada

Canada

From: Echeverria, Marietta [mailto:Echeverria.Marietta@epa.gov]
Sent: 2016-06-28 9:04 AM
To: Sterkenburg, Neilda (HC/SC)
Cc: Isbell, Diane
Subject: FW: review of flumethrin/imidicloprid pet collar

Hi Neilda,

I'm resending this in case you missed it. Susan Lewis is interested in having a conference call with you and Peter on this issue. I'm looping Diane Isbell in so she can help with scheduling. Is there anyone Diane should work with on this?

Thanks,
Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1
Registration Division
Office of Pesticide Programs
703-305-8578
http://www.epa.gov/pesticide-registration

From: Echeverria, Marietta
Sent: Tuesday, June 14, 2016 2:22 PM
To: 'neilda.sterkenburg@canada.ca' <neilda.sterkenburg@canada.ca>
Subject: review of flumethrin/imidicloprid pet collar

Greetings Neilda,

My name is Marietta Echeverria and I am a branch chief in the Registration Division of EPA's OPP. I met you when you were visiting a few months ago. Our reviewers in HED have been collaborating with your reviewers in HED on the review of incident data associated with the Bayer Seresto pet collar (combination of imidacloprid and flumethrin). We met with Bayer last week and I understand that you were meeting with them this week. Are you available for a phone call this week to discuss the status of the reviews?

Thanks,

Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1
Registration Division
Office of Pesticide Programs
703-305-8578
http://www.epa.gov/pesticide-registration

Message

From: Isbell, Diane [Isbell.Diane@epa.gov]
Sent: 6/29/2016 3:59:28 PM
To: Squires, Janice (HC/SC) [janice.squires@canada.ca]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]
CC: Sterkenburg, Neilda (HC/SC) [neilda.sterkenburg@canada.ca]
Subject: RE: review of flumethrin/imidicloprid pet collar

Thanks so much!

From: Squires, Janice (HC/SC) [mailto:janice.squires@canada.ca]
Sent: Wednesday, June 29, 2016 11:49 AM
To: Isbell, Diane <Isbell.Diane@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Sterkenburg, Neilda (HC/SC) <neilda.sterkenburg@canada.ca>
Subject: RE: review of flumethrin/imidicloprid pet collar

Hi Diane,

I've managed to get folks from PMRA for July 12, 3-4 p.m. I'll send an invite.

Janice

From: Isbell, Diane [mailto:Isbell.Diane@epa.gov]
Sent: 2016-06-29 11:16 AM
To: Squires, Janice (HC/SC); Echeverria, Marietta
Cc: Sterkenburg, Neilda (HC/SC)
Subject: RE: review of flumethrin/imidicloprid pet collar

Hi Janice,
Unfortunately, Susan isn't available either of those dates. Here are a couple of dates that look for both Susan and Marietta: 7/7 from 3 – 4 and 7/12 from 3 – 4. Marietta will be out of the office from 7/18 – 7/29 and Susan retires on 8/3. Sorry that it is so complicated.

Thanks for your help! Diane

÷ ÷
Diane Isbell
Special Assistant
Registration Division, 7505P
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460
703-308-8154

From: Squires, Janice (HC/SC) [mailto:janice.squires@canada.ca]
Sent: Wednesday, June 29, 2016 10:10 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Isbell, Diane <Isbell.Diane@epa.gov>; Sterkenburg, Neilda (HC/SC) <neilda.sterkenburg@canada.ca>
Subject: RE: review of flumethrin/imidicloprid pet collar

Hi Marietta,

Please let me know if you would be available:

July 13th, 3-4 p.m.
July 15th, anytime between 9:00-12 and 1:00-4:00

Thank you,
Janice

From: Echeverria, Marietta [mailto:Echeverria.Marietta@epa.gov]
Sent: 2016-06-28 2:12 PM
To: Sterkenburg, Neilda (HC/SC)
Cc: Isbell, Diane; Squires, Janice (HC/SC)
Subject: RE: review of flumethrin/imidicloprid pet collar

Hi Neilda,

Thank you for the update and I certainly understand the need to consult with counsel. We'll look for the email with possible dates for a phone call and go from there.

Cheers,
Marietta

From: Sterkenburg, Neilda (HC/SC) [mailto:neilda.sterkenburg@canada.ca]
Sent: Tuesday, June 28, 2016 12:06 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Isbell, Diane <Isbell.Diane@epa.gov>; Squires, Janice (HC/SC) <janice.squires@canada.ca>
Subject: RE: review of flumethrin/imidicloprid pet collar

Hi Marietta,

Sorry for not having replied to your email, I've had to consult our legal service with respect to what we can, and cannot, chat about on this file. We've shared the outcome of our reviews with Bayer CropScience, and they have asked explicitly that we not share our reviews with regulatory partners, thus the need for me to consult with legal.

I think a phone call is a good idea. I'm assuming that you would like Peter Chan on the call, however he'll be away for the month of July. Having said that, we'll arrange for either Yad Bhuller or Connie Moase to participate in the call. Also, it would be a good idea for Peter Brander (our Chief Registrar) to participate. I'll ask my assistant to come up with a few possible days and times asap and we'll be in touch.

Again, my apologies for not having replied, I just had to wait to chat with legal, which I just did late yesterday. Thanks for your understanding.

Regard,

Neilda

Neilda Sterkenburg
Director | Directrice
Review and Science Integration Division | Division des examens et de l'intégration scientifique
Pest Management Regulatory Agency | Agence règlementaire de la lutte antiparasitaire
Health Canada | Santé Canada

Suite E602, 2720 Riverside Drive,
Ottawa, ON Canada K1A OK9
neilda.sterkenburg@canada.ca
Telephone | Téléphone: 613-736-3851
Government of Canada | Gouvernement du Canada

Health Canada Santé Canada

Canada

From: Echeverria, Marietta [mailto:Echeverria.Marietta@epa.gov]
Sent: 2016-06-28 9:04 AM
To: Sterkenburg, Neilda (HC/SC)
Cc: Isbell, Diane
Subject: FW: review of flumethrin/imidicloprid pet collar

Hi Neilda,

I'm resending this in case you missed it. Susan Lewis is interested in having a conference call with you and Peter on this issue. I'm looping Diane Isbell in so she can help with scheduling. Is there anyone Diane should work with on this?

Thanks,
Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1
Registration Division
Office of Pesticide Programs
703-305-8578
http://www.epa.gov/pesticide-registration

From: Echeverria, Marietta
Sent: Tuesday, June 14, 2016 2:22 PM
To: 'neilda.sterkenburg@canada.ca' <neilda.sterkenburg@canada.ca>
Subject: review of flumethrin/imidicloprid pet collar

Greetings Neilda,

My name is Marietta Echeverria and I am a branch chief in the Registration Division of EPA's OPP. I met you when you were visiting a few months ago. Our reviewers in HED have been collaborating with your reviewers in HED on the review of incident data associated with the Bayer Seresto pet collar (combination of imidacloprid and flumethrin). We met with Bayer last week and I understand that you were meeting with them this week. Are you available for a phone call this week to discuss the status of the reviews?

Thanks,
Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1
Registration Division
Office of Pesticide Programs
703-305-8578

http://www.epa.gov/pesticide-registration

Message

From: Miller, David [Miller.DavidJ@epa.gov]
Sent: 5/25/2016 4:17:38 PM
To: Recore, Shanna [Recore.Shanna@epa.gov]; Sarkar, Bayazid [Sarkar.Bayazid@epa.gov]; Evans, Elizabeth [Evans.Elizabeth@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Nguyen, James [Nguyen.James@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Britton, Wade [Britton.Wade@epa.gov]; VanAlstine, Julie [VanAlstine.Julie@epa.gov]; Hawkins, Monica [Hawkins.Monica@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]
CC: Adler, Bonnie [Adler.Bonnie@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]
Subject: RE: Update -- and Discuss upcoming spot-on and Seresto activities and meetings
Attachments: Spot On Seresto slides for FDA meeting 4-18-16_send_update.pptx

Spot On Seresto slides for FDA m...

All,

There are several things we said we'd send out. These will need to go in pieces over today. But here's the first – the presentation we gave to FDA. This would serve as the basis of what we would plan on presenting to Bayer - note that

Ex. 5 Deliberative Process (DP)

But the attached may help in understanding some of the other stuff that was done, beyond what we spoke about today.

David.

-----Original Appointment-----
From: Miller, David
Sent: Sunday, May 22, 2016 5:39 PM
To: Miller, David; Recore, Shanna; Sarkar, Bayazid; Evans, Elizabeth; Rossmeisl, Colleen; Breeden-Alemi, Julie; Echeverria, Marietta; Nguyen, James; Davis, Kable; Britton, Wade; VanAlstine, Julie; Hawkins, Monica; Davis, Donna
Cc: Adler, Bonnie; Biscoe, Melanie; Arrington, Linda
Subject: Update -- and Discuss upcoming spot-on and Seresto activities and meetings
When: Wednesday, May 25, 2016 8:30 AM-9:30 AM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS10771/Potomac-Yard-One

See agenda and notes from Rick Kingston meeting attached

David.

<< File: Agenda and Notes from 5_13_16 Kingston meeting.docx >>

P.S. I promise not to oversleep this meeting ; -)

Message

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 9/7/2016 10:20:03 PM
To: Goodis, Michael [Goodis.Michael@epa.gov]
CC: Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]
Subject: Re: Heads up

This is in reference to the Seresto pet collar

Sent from my iPhone

On Sep 7, 2016, at 6:10 PM, Goodis, Michael <Goodis.Michael@epa.gov> wrote:

> What's the issue?
>
> Michael L. Goodis, P.E.
> Acting Director, Registration Division (RD)
> Office of Pesticide Programs (OPP)
>
> Phone 703-308-8157
> Room S7624
>
> ---
>
> **From:** Echeverria, Marietta
> **Sent:** Wednesday, September 07, 2016 6:06 PM
> **To:** Goodis, Michael <Goodis.Michael@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Vogel, Dana <Vogel.Dana@epa.gov>
> **Cc:** Arrington, Linda <Arrington.Linda@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>
> **Subject:** Fwd: Heads up
>
> FYI
>
> Sent from my iPhone
>
> Begin forwarded message:
>
>> **From:** Bruce Martin <bruce.martin@bayer.com>
>> **Date:** September 7, 2016 at 5:33:00 PM EDT
>> **To:** "Davis, Kable" <Davis.Kable@epa.gov>, "Echeverria, Marietta" <Echeverria.Marietta@epa.gov>
>> **Cc:** Doug Spilker <doug.spilker@bayer.com>, Bruce Martin <bruce.martin@bayer.com>
>> **Subject: Heads up**
>>
>> Bo and Marietta,
>> This is an advanced notice that Bayer's upper management and legal departments are contacting Ms. Yu-Ting Guilaran and Dr. Dana Vogel to request an audience at EPA the week of September 12. The request is to meet in accordance with the stakeholder engagement provisions of 40 CFR to understand the scope of the flumethrin report that is to be made public by the end of September. If you have questions please let me know.

Best regards,

Bruce Martin
Director, Regulatory Affairs
Animal Health Development, North America

Bayer: Science for A Better Life

Bayer Animal Health
Bayer HealthCare LLC
12809 Shawnee Mission Pkwy
Shawnee, KS 66216
USA

Tel: +1 913 268 2779
Fax: +1 913 268 2075
Mobile: +1 913 5235048
E-mail: bruce.martin@bayer.com
Web: http://www.bayer.com

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Message

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 4/21/2016 7:16:45 PM
To: Evans, Elizabeth [Evans.Elizabeth@epa.gov]
Subject: RE: PMRA Seresto update from conference call today

Ok, thanks.

From: Evans, Elizabeth
Sent: Thursday, April 21, 2016 3:01 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: RE: PMRA Seresto update from conference call today

Marietta- Shanna is out sick today and compressed tomorrow, so if she doesn't respond to you until Monday you'll know why.
I saw via the email exchange that Shanna did ask PRMA for their human health risk assessment for flumethrin. The response was – they want to clean it up a bit before sharing it with us. Apparently the assessment was either recently final or it is still under development.

Liz

From: Echeverria, Marietta
Sent: Thursday, April 21, 2016 1:55 PM
To: Recore, Shanna <Recore.Shanna@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden, Julie <Breeden.Julie@epa.gov>
Cc: Evans, Elizabeth <Evans.Elizabeth@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>; Davis, Donna <Davis.Donna@epa.gov>; Adler, Bonnie <Adler.Bonnie@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Arrington, Linda <Arrington.Linda@epa.gov>
Subject: RE: PMRA Seresto update from conference call today

David et al.,
I spoke with Donna Davis this morning. She is having her team write up a brief technical summary (1-2 paragraphs) describing the endpoints. Ex. 5 Deliberative Process (DP) Ex. 5 Deliberative Process (DP) Ex. 5 Deliberative Process (DP) Ex. 5 Deliberative Process (DP). PRD is hosting a call with Bayer tomorrow on this issue.

Shanna, Did PMRA say when they could share the assessment?

Thanks,
Marietta

From: Recore, Shanna
Sent: Wednesday, April 20, 2016 8:53 PM
To: Miller, David <Miller.DavidJ@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden, Julie <Breeden.Julie@epa.gov>
Cc: Evans, Elizabeth <Evans.Elizabeth@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>
Subject: RE: PMRA Seresto update from conference call today

Vicky (from PMRA) also said that they will be in touch next week, after the second director meeting, to schedule a conference call regarding PMRA's decision. She said the meeting will be on Thursday but she is not sure if it will be morning or afternoon.

From: Miller, David
Sent: Wednesday, April 20, 2016 4:31 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden, Julie <Breeden.Julie@epa.gov>
Cc: Recore, Shanna <Recore.Shanna@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>
Subject: FW: PMRA Seresto update from conference call today

Just FYI – see below

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

David.

From: Recore, Shanna
Sent: Wednesday, April 20, 2016 2:55 PM
To: Miller, David <Miller.DavidJ@epa.gov>; Crowley, Matthew <Crowley.Matthew@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: FW: PMRA Seresto update from conference call today

I had a voicemail from Vicky Godfrey from PMRA when I got back to my desk. She said that they had the directors meeting today and that the directors agreed that the collar should not be registered.

From: Recore, Shanna
Sent: Tuesday, April 19, 2016 12:55 PM
To: Miller, David <Miller.DavidJ@epa.gov>
Cc: Evans, Elizabeth <evans.elizabeth@epa.gov>
Subject: PMRA Seresto update from conference call today

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Follow-up action items:

Vicky from PRMA is going to call me tomorrow after the management meeting to give an update.

PMRA is going to, over the next couple weeks, send us the causality analysis, the updated plausibility analysis, and arrange another conference call after a 2nd management meeting that they anticipate taking place next week.

Shanna Recore
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
(703) 308-9399

Message

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 4/19/2016 7:03:23 PM
To: Breeden, Julie [Breeden.Julie@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]
Subject: FW: seresto collar
Attachments: D385628.mem.doc; D392125.mem.docx

From: Recore, Shanna
Sent: Tuesday, April 19, 2016 2:57 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>
Subject: seresto collar

Flumethrin is RAB VI (Donna Davis)
Imidacloprid is RAB I (Billy Smith)

RAB I did the pet collar ORE assessment for imidacloprid. I cannot find an ORE assessment for flumethrin. But the residential exposure for flumethrin (also done by RAB I) is reviewed in the "Flumethrin: Human Health Risk Assessment for the Section 3 Registration Action for Cat and Dog Collars" Both documents are Attached.

Shanna Recore
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
(703) 308-9399

Appointment

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 5/3/2016 2:18:42 PM
To: Recore, Shanna [Recore.Shanna@epa.gov]

Subject: Accepted: update regarding spot-ons and seresto
Location: DCRoomPYS10771/Potomac-Yard-One

Start: 5/5/2016 1:00:00 PM
End: 5/5/2016 2:00:00 PM
Show Time As: Busy

Thanks for setting this up. I will also forward to the PRD team since flumethrin is in reg-review.

Message

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 5/3/2016 2:34:33 PM
To: Recore, Shanna [Recore.Shanna@epa.gov]
Subject: RE: update regarding spot-ons and seresto

Ok, thanks

From: Recore, Shanna
Sent: Tuesday, May 03, 2016 10:26 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: RE: update regarding spot-ons and seresto

Okay. I just want to clarify, I don't anticipate having any additional information from PMRA. But we are having a conference call with FDA on Wednesday regarding our spot-on template. So hopefully some news there.

-----Original Appointment-----
From: Echeverria, Marietta
Sent: Tuesday, May 03, 2016 10:19 AM
To: Recore, Shanna
Subject: Accepted: update regarding spot-ons and seresto
When: Thursday, May 05, 2016 9:00 AM-10:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS10771/Potomac-Yard-One

Thanks for setting this up. I will also forward to the PRD team since flumethrin is in reg-review.

Message

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 6/9/2016 11:57:52 AM
To: Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]
Subject: FW: Bayer Slides
Attachments: Seresto slides for Bayer meeting 6-9-16 (002)_BS_6_8_16 sr_DJM.pptx

Can we meet briefly to review and get them comments? I have time now until 9 am.

From: Miller, David
Sent: Wednesday, June 08, 2016 4:05 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Davis, Kable <Davis.Kable@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>
Cc: Sarkar, Bayazid <Sarkar.Bayazid@epa.gov>; Recore, Shanna <Recore.Shanna@epa.gov>; Nguyen, James <Nguyen.James@epa.gov>; Evans, Elizabeth <Evans.Elizabeth@epa.gov>
Subject: Bayer Slides

Still finalizing these up, but here's the meat.

I'm here for a while if you want to talk. I will send around second draft later tonight for review tomorrow.

We probably want to add in a few slides regarding **Ex. 5 Deliberative Process (DP)** Shanna can add those in tomorrow am – she is at at 6 am.

David J. Miller CAPT | USPHS
Chief, Chemistry & Exposure Branch
and Acting Chief, Toxicology & Epidemiology Branch
Health Effects Division
Office of Pesticide Programs
703-305-5352 (voice)
703-305-5147 (fax)

Visit www.epa.gov/pesticides

Message

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 5/27/2016 5:02:08 PM
To: Davis, Kable [Davis.Kable@epa.gov]
Subject: RE: Seresto thoughts

Thanks! Have a great weekend!

-----Original Message-----
From: Davis, Kable
Sent: Friday, May 27, 2016 1:01 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: RE: Seresto thoughts

Hi Marietta -

Below is the contact information for the person we are calling next week regarding Seresto. I thought you may want it for your records.

Dana Bruce
Manager, Incident Reporting Program
Pest Management Regulatory Agency,
Health Canada / Government of Canada
Tel: 613-736-3479

See you next week.
Bo

-----Original Message-----
From: Echeverria, Marietta
Sent: Friday, May 27, 2016 6:46 AM
To: Davis, Kable <Davis.Kable@epa.gov>
Subject: Seresto thoughts

It would seem Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

I want to talk to PMRA next week before the bayer meeting. Do you know who my counterpart is in the registration directorate?

Sent from my iPhone

Message

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 7/6/2016 1:05:31 PM
To: Arrington, Linda [Arrington.Linda@epa.gov]
Subject: FW: Seresto - Proposed Studies for Discussion with PMRA

FYI

From: Davis, Kable
Sent: Wednesday, July 06, 2016 5:39 AM
To: Davis, Donna <Davis.Donna@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Britton, Wade <Britton.Wade@epa.gov>; Adler, Bonnie <Adler.Bonnie@epa.gov>; Biscoe, Melanie <Biscoe.Melanie@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Breeden-Alemi, Julie <Breeden-Alemi.Julie@epa.gov>; Backus, Byron <Backus.Byron@epa.gov>
Subject: FW: Seresto - Proposed Studies for Discussion with PMRA

Everyone –

Ex. 5 Deliberative Process (DP)

Bayer will submit protocol, via a PRIA action, for the third study. We'll need to discuss at some point who should review it.

Let me know if you have any questions.

Enjoy the day.
Bo

From: Doug Spilker [mailto:doug.spilker@bayer.com]
Sent: Tuesday, July 05, 2016 12:37 PM
To: Davis, Kable <Davis.Kable@epa.gov>
Cc: Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Bruce Martin <bruce.martin@bayer.com>
Subject: Seresto - Proposed Studies for Discussion with PMRA

Dear Mr. Kable,

As discussed in the teleconference between Bayer Animal Health and EPA on June 30th, Bayer will be proposing additional studies that should provide data to assist PMRA in refining their draft evaluations. The proposed studies that will be discussed with PMRA in the next few weeks include:

1. Dermal penetration study(ies) with flumethrin
2. Hand-to-mouth exposure assessment following dog stroking

3. Short-term animal safety study with a pharmacokinetic component evaluating earlier blood concentrations of the active ingredients, where previous studies did not demonstrate blood concentrations at less than 7 days post-collar application.
4. Pharmacokinetic studies in rodents at doses, especially NOEL, used in the laboratory oral tox studies.

   The goal of studies #3 and 4 will be to compare systemic exposure in dogs following collar application compared to systemic exposure in the laboratory oral tox studies. That is, does the systemic exposure following collar application justify the plausibility assessment?

After agreement in principle regarding the studies that PMRA would find useful to refine their assessments of Seresto, we will present this information to EPA, as well. Any protocols sent to PMRA for review, will also be sent concurrently to EPA for timely review. Because PMRA wants the additional studies to begin as soon as possible, the protocol reviews (and amendment cycles, if needed) must be completed as soon as possible.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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Message

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 6/28/2016 4:37:58 PM
To: Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]
Subject: FW: review of flumethrin/imidicloprid pet collar

FYI

From: Sterkenburg, Neilda (HC/SC) [mailto:neilda.sterkenburg@canada.ca]
Sent: Tuesday, June 28, 2016 12:06 PM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Isbell, Diane <Isbell.Diane@epa.gov>; Squires, Janice (HC/SC) <janice.squires@canada.ca>
Subject: RE: review of flumethrin/imidicloprid pet collar

Hi Marietta,

Sorry for not having replied to your email, I've had to consult our legal service with respect to what we can, and cannot, chat about on this file. We've shared the outcome of our reviews with Bayer CropScience, and they have asked explicitly that we not share our reviews with regulatory partners, thus the need for me to consult with legal.

I think a phone call is a good idea. I'm assuming that you would like Peter Chan on the call, however he'll be away for the month of July. Having said that, we'll arrange for either Yad Bhuller or Connie Moase to participate in the call. Also, it would be a good idea for Peter Brander (our Chief Registrar) to participate. I'll ask my assistant to come up with a few possible days and times asap and we'll be in touch.

Again, my apologies for not having replied, I just had to wait to chat with legal, which I just did late yesterday. Thanks for your understanding.

Regard,

Neilda

Neilda Sterkenburg
Director | Directrice
Review and Science Integration Division | Division des examens et de l'intégration scientifique
Pest Management Regulatory Agency | Agence règlementaire de la lutte antiparasitaire
Health Canada | Santé Canada
Suite E602, 2720 Riverside Drive,
Ottawa, ON Canada K1A OK9
neilda.sterkenburg@canada.ca
Telephone | Téléphone: 613-736-3851
Government of Canada | Gouvernement du Canada

Health Canada Santé Canada

Canada

From: Echeverria, Marietta [mailto:Echeverria.Marietta@epa.gov]
Sent: 2016-06-28 9:04 AM
To: Sterkenburg, Neilda (HC/SC)
Cc: Isbell, Diane
Subject: FW: review of flumethrin/imidicloprid pet collar

Hi Neilda,

I'm resending this in case you missed it. Susan Lewis is interested in having a conference call with you and Peter on this issue. I'm looping Diane Isbell in so she can help with scheduling. Is there anyone Diane should work with on this?

Thanks,
Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1
Registration Division
Office of Pesticide Programs
703-305-8578
http://www.epa.gov/pesticide-registration

From: Echeverria, Marietta
Sent: Tuesday, June 14, 2016 2:22 PM
To: 'neilda.sterkenburg@canada.ca' <neilda.sterkenburg@canada.ca>
Subject: review of flumethrin/imidicloprid pet collar

Greetings Neilda,

My name is Marietta Echeverria and I am a branch chief in the Registration Division of EPA's OPP. I met you when you were visiting a few months ago. Our reviewers in HED have been collaborating with your reviewers in HED on the review of incident data associated with the Bayer Seresto pet collar (combination of imidacloprid and flumethrin). We met with Bayer last week and I understand that you were meeting with them this week. Are you available for a phone call this week to discuss the status of the reviews?

Thanks,
Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1
Registration Division
Office of Pesticide Programs
703-305-8578
http://www.epa.gov/pesticide-registration

Message

From: Echeverria, Marietta [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=36C56B7169144626BD6AADEA25992D4E-MARIETTA ECHEVERRIA]
Sent: 6/28/2016 3:49:13 PM
To: Isbell, Diane [Isbell.Diane@epa.gov]
CC: Herndon, George [Herndon.George@epa.gov]
Subject: RE: review of flumethrin/imidicloprid pet collar

THANK YOU!

From: Isbell, Diane
Sent: Tuesday, June 28, 2016 11:49 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Cc: Herndon, George <Herndon.George@epa.gov>
Subject: RE: review of flumethrin/imidicloprid pet collar

Ok, I will do it.

From: Echeverria, Marietta
Sent: Tuesday, June 28, 2016 11:43 AM
To: Isbell, Diane <Isbell.Diane@epa.gov>
Cc: Herndon, George <Herndon.George@epa.gov>
Subject: RE: review of flumethrin/imidicloprid pet collar

Thanks, Diane. Jeff, thought you might be able to help facilitate. If not, I will work on it directly. Let me know. Thanks again.

From: Isbell, Diane
Sent: Tuesday, June 28, 2016 9:58 AM
To: Echeverria, Marietta <Echeverria.Marietta@epa.gov>
Subject: RE: review of flumethrin/imidicloprid pet collar

You can work with Janice Squires at PMRA, she keeps Neilda's calendar. Her email is: janice.squires@canada.ca

---

From: Echeverria, Marietta
Sent: Tuesday, June 28, 2016 9:04 AM
To: neilda.sterkenburg@canada.ca
Cc: Isbell, Diane <Isbell.Diane@epa.gov>
Subject: FW: review of flumethrin/imidicloprid pet collar

Hi Neilda,

I'm resending this in case you missed it. Susan Lewis is interested in having a conference call with you and Peter on this issue. I'm looping Diane Isbell in so she can help with scheduling. Is there anyone Diane should work with on this?

Thanks,
Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1

Registration Division
Office of Pesticide Programs
703-305-8578
http://www.epa.gov/pesticide-registration

From: Echeverria, Marietta
Sent: Tuesday, June 14, 2016 2:22 PM
To: 'neilda.sterkenburg@canada.ca' <neilda.sterkenburg@canada.ca>
Subject: review of flumethrin/imidicloprid pet collar

Greetings Neilda,

My name is Marietta Echeverria and I am a branch chief in the Registration Division of EPA's OPP. I met you when you were visiting a few months ago. Our reviewers in HED have been collaborating with your reviewers in HED on the review of incident data associated with the Bayer Seresto pet collar (combination of imidacloprid and flumethrin). We met with Bayer last week and I understand that you were meeting with them this week. Are you available for a phone call this week to discuss the status of the reviews?

Thanks,
Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1
Registration Division
Office of Pesticide Programs
703-305-8578
http://www.epa.gov/pesticide-registration

Appointment

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 9/23/2016 3:39:29 PM
To: Davis, Kable [Davis.Kable@epa.gov]; Goodis, Michael [Goodis.Michael@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Knorr, Michele [Knorr.Michele@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]

Subject: Seresto (flumethrin); 6(a)(2) letter discussion
Location: DCRoomPYS7621B/Potomac-Yard-One

Start: 9/26/2016 1:00:00 PM
End: 9/26/2016 1:30:00 PM
Show Time As: Busy

Required Attendees: Goodis, Michael; Guilaran, Yu-Ting; Vogel, Dana; Knorr, Michele; Perlis, Robert; Echeverria, Marietta; Arrington, Linda; Miller, David; Biscoe, Melanie; Piansay, Maria; Breeden-Alemi, Julie

During our last discussion regarding next steps for dealing with the Seresto incidents, it was suggested that we could write a 6(a)(2) letter. Let's meet and discuss this potential path forward in greater detail. This time slot isn't perfect, however it worked for the greatest number of people. Below is the call-in information.

Call-in No:
Conf. Code: **Ex. 6 PP - conference code/call in number**

Appointment

From: Piansay, Maria [Piansay.Maria@epa.gov]
Sent: 9/13/2016 6:51:30 PM
To: Piansay, Maria [Piansay.Maria@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]
CC: Knorr, Michele [knorr.michele@epa.gov]; Goodis, Michael [Goodis.Michael@epa.gov]

Subject: Flumethrin Bayer Meeting
Location: DCRoomPYS9261/Potomac-Yard-One

Start: 9/22/2016 6:00:00 PM
End: 9/22/2016 7:00:00 PM
Show Time As: Busy

Required Attendees: Guilaran, Yu-Ting; Vogel, Dana; Rosenblatt, Daniel; Echeverria, Marietta; Miller, David; Rossmeisl, Colleen; Arrington, Linda; Davis, Kable; Biscoe, Melanie
Optional Attendees: Knorr, Michele; Goodis, Michael

Meeting Agenda from Bayer

1. To discuss status and timing of the documents EPA intends to release in September regarding Flumethrin and the Flumethrin-containing products;
2. To review timing of registration review for the Flumethrin-containing products and inclusion in the pyrethroid registration review;
3. To understand references and approach in these documents to Seresto;
4. To express Bayer's perspective on potential references to Flumethrin and Seresto;
5. To understand the anticipated scope of the registration review, and the expected schedule for the conduct of the review;
6. For Bayer to understand from the Agency its intentions and next steps in this process.

Attending from Bayer will be:

- Joyce Lee, President, Commercial Operations North America, Bayer Animal Health
- Robert Zolynas, Vice President Research and Development, North America, Bayer Animal Health
- Jessica Monachello, Assistant General Counsel Bayer Animal Health
- Roger R. Martella Jr., Outside Counsel, Sidley Austin LLP

Appointment

From: Housenger, Jack [Housenger.Jack@epa.gov]
Sent: 9/13/2016 9:08:20 PM
To: Housenger, Jack [Housenger.Jack@epa.gov]; Goodis, Michael [Goodis.Michael@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Knorr, Michele [Knorr.Michele@epa.gov]; Keigwin, Richard [Keigwin.Richard@epa.gov]
CC: Perlis, Robert [Perlis.Robert@epa.gov]

Subject: Seresto Pet Collar Briefing
Attachments: Seresto Briefing Document.docx
Location: 12100 PY

Start: 9/20/2016 3:00:00 PM
End: 9/20/2016 4:00:00 PM
Show Time As: Busy

Required Attendees: Goodis, Michael; Echeverria, Marietta; Davis, Kable; Rosenblatt, Daniel; Guilaran, Yu-Ting; Arrington, Linda; Biscoe, Melanie; Piansay, Maria; Vogel, Dana; Miller, David; Rossmeisl, Colleen; Knorr, Michele; Keigwin, Richard
Optional Attendees: Perlis, Robert

9/20/16 Update:

Good morning,

Please see the one-pager attached, and note that the meeting will be held in room 12100.

Briefing with Jack regarding an upcoming meeting with Bayer about the Seresto pet collar preceding the meeting with Bayer to take place on Thursday, September 22nd. A one-pager will be forthcoming and added to this invitation.

Meeting requested by Kable Bo Davis on 9/13/16
Scheduled by Shannon Jewell

EPA-internal, confidential, deliberative

Seresto Briefing Document

Product Description

- Seresto is a dog and cat collar, which is intended to control fleas and ticks for up to 8 months.
- The collar contains 4.5% flumethrin and 10.0% imidacloprid. This is the only use for flumethrin.

Timeline

- **July 27, 2015:** EPA received a press inquiry alerting us to an alleged high number of reported pet incidents.
- **August 5, 2015:** Bayer submitted sales information for Seresto.
- **August 28, 2015:** Bayer submitted incident data using template suggested by EPA.
- **December 16, 2015:** RD and HED briefed upper management on the status of review for the incident data.
- **July 18, 2016:** OPP received the incident report outlining the overall findings and conclusions of PMRA's Seresto collar review.
- **August 10, 2016:** OPP was informed, via conference call, that PMRA would not register Seresto in Canada. As a result, Bayer withdrew the submission and requested PMRA not share any further documents with EPA.
- **September 1, 2016:** OPP completes its draft review of the incident data and PMRA's causality analysis. The document has not been finalized.
- **September 2, 2016:** EPA receives Bayer's critique of PMRA's Animal Incident Assessment. The document is in the process of being reviewed.
- **September 22, 2016:** Bayer has requested a meeting with EPA to discuss the scope of the flumethrin report that is to be made public by the end of September for Registration Review.

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP) - Ex. 4 Potential CBI

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Note – OGC is attending to address any legal concerns.

Appointment

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 9/9/2016 1:13:52 PM
To: Davis, Kable [Davis.Kable@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Piansay, Maria [Piansay.Maria@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]

Subject: Bayer (Seresto) Pre-Meeting
Location: DCRoomPYS7621B/Potomac-Yard-One

Start: 9/12/2016 6:30:00 PM
End: 9/12/2016 7:00:00 PM
Show Time As: Busy

Required Attendees: Guilaran, Yu-Ting; Vogel, Dana; Dan Rosenblatt; Arrington, Linda; Biscoe, Melanie; Piansay, Maria; Echeverria, Marietta

Let's meet and prepare for the upcoming meeting with Bayer regarding flumethrin (Seresto).

Call-in No: Ex. 6 PP - conference code/call in number
Conf. Code:

Appointment

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 8/11/2016 8:51:40 PM
To: Davis, Kable [Davis.Kable@epa.gov]; Goodis, Michael [Goodis.Michael@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]; Recore, Shanna [Recore.Shanna@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]

Subject: Seresto Discussion
Attachments: Seresto DD Briefing final draft.pptx
Location: DCRoomPYS7100/Potomac-Yard-One

Start: 8/16/2016 12:00:00 PM
End: 8/16/2016 1:00:00 PM
Show Time As: Busy

Required Attendees: Goodis, Michael; Vogel, Dana; Guilaran, Yu-Ting; Echeverria, Marietta; Arrington, Linda; Miller, David; Rossmeisl, Colleen; Recore, Shanna; Breeden-Alemi, Julie; Biscoe, Melanie

Everyone –

HED has been reviewing the incident data for Seresto (EPA Reg. No. 11556-155) for the last year and the objective of this meeting is to discuss the appropriate next steps. The product was pending review in Canada, however was withdrawn last week. To remind everyone of the situation, I have attached the slides from the DD briefing which was given last December.

I apologize for the early meeting, however this time worked best for the majority of people.

Seresto DD Briefing final draf...

Appointment

From: Davis, Kable [Davis.Kable@epa.gov]
Sent: 8/1/2016 1:51:02 PM
To: Davis, Kable [Davis.Kable@epa.gov]; Goodis, Michael [Goodis.Michael@epa.gov]; Rosenblatt, Daniel [Rosenblatt.Dan@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Breeden-Alemi, Julie [Breeden-Alemi.Julie@epa.gov]

Subject: Seresto Briefing
Attachments: Seresto DD Briefing final draft.pptx
Location: DCRoomPYS7621B/Potomac-Yard-One

Start: 8/11/2016 1:00:00 PM
End: 8/11/2016 2:00:00 PM
Show Time As: Busy

Required Attendees: Goodis, Michael; Dan Rosenblatt; Echeverria, Marietta; Breeden-Alemi, Julie

IVB1 would like to brief the IO on the status of review for the incident data reported for Seresto (EPA Reg. No. 11556-155). The collar contains flumethrin and imidacloprid and is intended to control flea and ticks on cats and dogs for up to 8 months. The investigation into these incidents began last summer via a press inquiry. The product is currently pending registration in Canada.

Please find attached the slides from the DD briefing, which was given back in December. We will also take this opportunity to update you on the status of our review since the last briefing.

Seresto DD Briefing final draf...

Appointment

From: Adler, Bonnie [Adler.Bonnie@epa.gov]
Sent: 8/1/2016 5:41:16 PM
To: Adler, Bonnie [Adler.Bonnie@epa.gov]; Arrington, Linda [Arrington.Linda@epa.gov]; Atwood, Donald [Atwood.Donald@epa.gov]; Biscoe, Melanie [Biscoe.Melanie@epa.gov]; Britton, Wade [Britton.Wade@epa.gov]; Cook, Colwell [cook.colwell@epa.gov]; Craig, Evisabel [Craig.Evisabel@epa.gov]; Davis, Donna [Davis.Donna@epa.gov]; Davis, Kable [Davis.Kable@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; English, LisaRenee [English.LisaRenee@epa.gov]; Hanson, Charmaine [Hanson.Charmaine@epa.gov]; Hawkins, Monica [Hawkins.Monica@epa.gov]; Holmes, Jean [Holmes.Jean@epa.gov]; VanAlstine, Julie [VanAlstine.Julie@epa.gov]; White, Katrina [White.Katrina@epa.gov]

Subject: Flumethrin TEAM meeting on Seresto - HED update - call in info below...
Location: DCRoomPYS9261/Potomac-Yard-One

Start: 8/4/2016 1:00:00 PM
End: 8/4/2016 2:00:00 PM
Show Time As: Busy

Required Attendees: Arrington, Linda; Atwood, Donald; Biscoe, Melanie; Britton, Wade; Cook, Colwell; Craig, Evisabel; Davis, Donna; Davis, Kable; Echeverria, Marietta; English, LisaRenee; Hanson, Charmaine; Hawkins, Monica; Holmes, Jean; VanAlstine, Julie; White, Katrina

Hi Folks,
HED has requested to meet to discuss this case and I wanted to gather the team for this conversation.
It may not take a whole hour, we'll see.
Thanks!
Bonnie

Call in- Ex. 6 PP - conference code/call in number conf code Ex. 6 PP - conference code/call in number
Thanks!

Appointment

From: Sterkenburg, Neilda (HC/SC) [neilda.sterkenburg@canada.ca]
Sent: 6/29/2016 3:55:52 PM
To: Sterkenburg, Neilda (HC/SC) [neilda.sterkenburg@canada.ca]; Isbell, Diane [Isbell.Diane@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Brander, Peter (HC/SC) [peter.brander@canada.ca]; Bhuller, Yadvinder (HC/SC) [yadvinder.bhuller@canada.ca]; Silva, Minoli (HC/SC) [minoli.silva@canada.ca]; Bruce, Dana (HC/SC) [dana.bruce@canada.ca]; Thomas, Monique (HC/SC) [monique.thomas@canada.ca]; Griffith, Anne (HC/SC) [anne.griffith@canada.ca]; Linke, Brenda (HC/SC) [brenda.linke@canada.ca]

Subject: Conference call with EPA: review of flumethrin/imidicloprid pet collar
Location: D620 (Dial (loca Ex. 6 – Conference Code Toll Free: Ex. 6 PP - conference code/call in number Conference ID: Ex. 6 PP - conference code/call in number

Start: 7/12/2016 7:00:00 PM
End: 7/12/2016 8:00:00 PM
Show Time As: Busy

Recurrence: (none)

From: Echeverria, Marietta
Sent: Tuesday, June 14, 2016 2:22 PM
To: 'neilda.sterkenburg@canada.ca' <neilda.sterkenburg@canada.ca>
Subject: review of flumethrin/imidicloprid pet collar
Greetings Neilda,
My name is Marietta Echeverria and I am a branch chief in the Registration Division of EPA's OPP. I met you when you were visiting a few months ago. Our reviewers in HED have been collaborating with your reviewers in HED on the review of incident data associated with the Bayer Seresto pet collar (combination of imidacloprid and flumethrin). We met with Bayer last week and I understand that you were meeting with them this week. Are you available for a phone call this week to discuss the status of the reviews?
Thanks,
Marietta

Marietta Echeverria, Chief
Invertebrate & Vertebrate Branch 1
Registration Division
Office of Pesticide Programs
703-305-8578
http://www.epa.gov/pesticide-registration

Message

From: Mastrota, Nicholas [Mastrota.Nicholas@epa.gov]
Sent: 3/4/2021 1:30:56 PM
To: Aubee, Catherine [Aubee.Catherine@epa.gov]; Wire, Cindy [Wire.Cindy@epa.gov]; Berckes, Nicole [Berckes.Nicole@epa.gov]; Miller, Robert [Miller.Robert@epa.gov]; Rust, Mary [Rust.Mary@epa.gov]
CC: Smith, Kimberly [Smith.Kimberly@epa.gov]; Wormell, Lance [Wormell.Lance@epa.gov]; Hopkins, Yvette [Hopkins.Yvette@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; Picone, Kaitlin [Picone.Kaitlin@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Panger, Melissa [Panger.Melissa@epa.gov]; Rossmeisl, Colleen [Rossmeisl.Colleen@epa.gov]
Subject: Canine Review "Collar-Gate" story

Good morning all,

The Canine Review is doing an investigation into Seresto collars and the EPA's handling of it. They have a story coming out soon titled "Collar-Gate": https://thecaninereview.com/

Ex. 5 Deliberative Process (DP)

Nick Mastrota

From: Aubee, Catherine <Aubee.Catherine@epa.gov>
Sent: Wednesday, March 03, 2021 2:17 PM
To: Wire, Cindy <Wire.Cindy@epa.gov>; Mastrota, Nicholas <Mastrota.Nicholas@epa.gov>; Berckes, Nicole <Berckes.Nicole@epa.gov>; Miller, Robert <Miller.Robert@epa.gov>; Rust, Mary <Rust.Mary@epa.gov>
Cc: Smith, Kimberly <Smith.Kimberly@epa.gov>; Wormell, Lance <Wormell.Lance@epa.gov>; Hopkins, Yvette <Hopkins.Yvette@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Picone, Kaitlin <Picone.Kaitlin@epa.gov>; Pease, Anita <Pease.Anita@epa.gov>; Panger, Melissa <Panger.Melissa@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>
Subject: RE: Flumethrin Question

That works for me – thank you. Mary and Greg's team can coordinate as appropriate with the different OPP divisions.

Best,
Catherine
Associate Director
OPP Registration Division
US Environmental Protection Agency

Contact:
Aubee.catherine@epa.gov
Mobile: 571.317.4402

From: Wire, Cindy <Wire.Cindy@epa.gov>
Sent: Wednesday, March 03, 2021 2:01 PM

To: Mastrota, Nicholas <Mastrota.Nicholas@epa.gov>; Berckes, Nicole <Berckes.Nicole@epa.gov>; Miller, Robert <Miller.Robert@epa.gov>; Rust, Mary <Rust.Mary@epa.gov>
Cc: Smith, Kimberly <Smith.Kimberly@epa.gov>; Wormell, Lance <Wormell.Lance@epa.gov>; Hopkins, Yvette <Hopkins.Yvette@epa.gov>; Aubee, Catherine <Aubee.Catherine@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Picone, Kaitlin <Picone.Kaitlin@epa.gov>; Pease, Anita <Pease.Anita@epa.gov>; Panger, Melissa <Panger.Melissa@epa.gov>; Rossmeisl, Colleen <Rossmeisl.Colleen@epa.gov>
Subject: RE: Flumethrin Question

All,

Region 9 is starting to get inquiries. As a result, they plan to direct public inquiries to Mary as the OPP Ombudsman, and press inquiries to Greg Siedschlag unless we advise them differently. FYI

Cindy Wire
PREP Coordinator & Region, State, Tribal Liaison
US EPA Office of Chemical Safety & Pollution Prevention
San Francisco, CA
Phone: 415-947-4242