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

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: September 17, 2019

SUBJECT: **Flumethrin**: Tier I Update Review of Human Incidents and Epidemiology for Proposed Interim Decision

PC Code: 036007
Decision No.: 555349
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
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DP Barcode: D454235
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Summary and Conclusions

Flumethrin incidents were previously reviewed in 2016 (S. Recore and E. Evans, D435503, 9/7/2016). At that time, the Agency stated that it would continue to monitor the incident data due to the fact that the only flumethrin end use product (Seresto Collar, Registration No. 11556-155) was a relatively new product that was registered on March 16, 2012..

In the current IDS analysis from January 1, 2016 to August 27, 2019, 252 flumethrin human incidents were reported to Main IDS; there were 374 flumethrin human incidents reported to

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Aggregate IDS. A query of SENSOR-Pesticides 1998-2015 identified three cases involving flumethrin. A query of NPIC from 2016 to August 14, 2019, identified three flumethrin cases.

The Agricultural Health Study (AHS) is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA. Flumethrin is not included in the AHS, and therefore this study does not provide information for this report.

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. Pesticide Re-Evaluation Division's, RMIB 5 has requested that TEB conduct a Tier I Update review summary of recent incident data from IDS, SENSOR, and NPIC. 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.

It is important to remember that 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, and such data should be interpreted with caution. Nonetheless, 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. Epidemiology studies can also be useful and 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, which also contains imidacloprid, is an eight-month collar used on dogs and cats for flea and tick control.

For this evaluation, both OPP Incident Data System (IDS), the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event

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Notification System for Occupational Risk-Pesticides (SENSOR) and 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.

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 generally contains incidents resulting in higher severity outcomes and provides more detail with regard to case specifics.[1] 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 for the three years from January 1, 2016 to August 27, 2019, there were 252 incidents reported that involved the active ingredient flumethrin. Nineteen of these incidents were classified as major severity. Narrative information for these 19 incidents and is found in Appendix A. Two hundred and thirty-three incidents were classified as moderate severity.

For the Aggregate IDS for the three years from January 1, 2016 to August 27, 2019, there were 374 incidents reported involving flumethrin. These incidents were classified as minor severity.

All the incidents reported to IDS involved Registration No. 11556-155 (Seresto Collar) which contains 4.5% flumethrin and 10% imidacloprid. Seresto Collar is used in dogs and cats to control fleas and ticks.

The total number of flumethrin incidents reported to Main and Aggregate IDS, from 2013 to 2018, appears to be increasing over time (Figure 1).

[1] Occasionally, low severity incidents are self-reported by the consumer directly to Main IDS.

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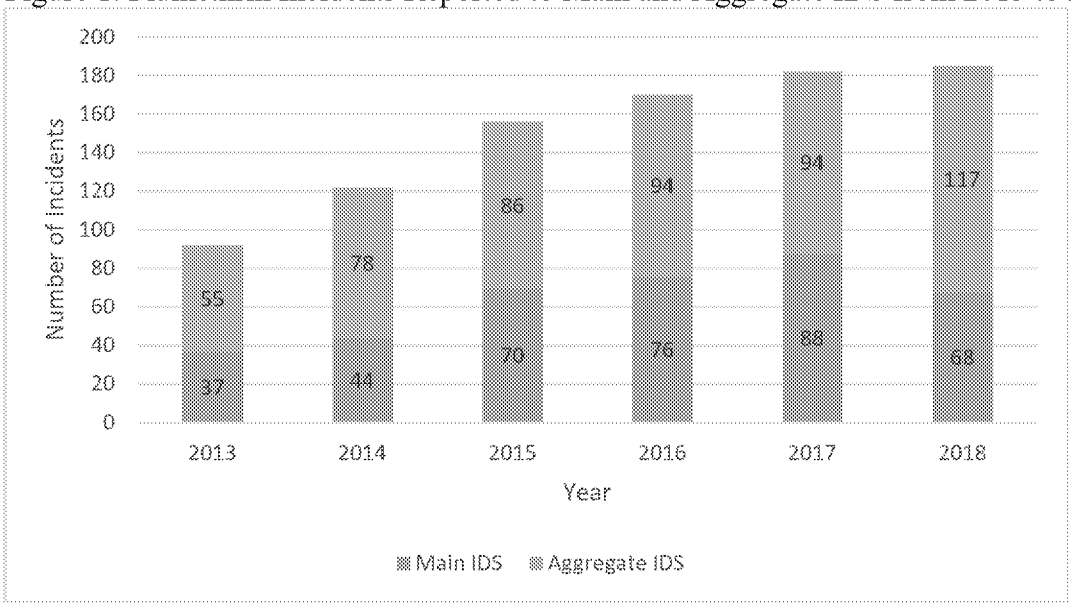
Figure 1. Flumethrin Incidents Reported to Main and Aggregate IDS from 2013 to 2018



Of the 19 major severity incidents that were further reviewed, the symptoms most often reported were dermal (n=8) and neurological (n=7). Note that a patient could exhibit multiple symptoms. Dermal symptoms reported include rash, redness, skin lesions, hives, and pruritus. Neurological symptoms reported include headaches, numbness, tingling and one person reported seizures.

b. SENSOR-Pesticides

The Center for Disease Control's National Institute for Occupational Safety and Health (CDC/NIOSH) manages a pesticide surveillance program and database entitled the Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides.[2] All cases must report at least two adverse health effects. Evidence for each case is evaluated for its causal relationship between exposure and illness based on the NIOSH case classification index.[3] Using standardized protocol and case definitions, SENSOR-Pesticides state coordinators, operating out of the state's department of health, receive state pesticide incident reports from local sources, then follow up with case sources to get incident scenario to obtain medical records and verify exposure scenario information.[4] This database includes pesticide illness case reports from multiple states from 1998-2015.[5]

A query of SENSOR-Pesticides from 2013-2015 identified three cases involving flumethrin. The three incidents were classified as low severity and are described in Appendix B.

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[2] SENSOR-Pesticides webpage: http://www.cdc.gov/niosh/topics/pesticides/overview.html.
[3] https://www.cdc.gov/niosh/topics/pesticides/pdfs/casedef.pdf
[4] https://www.cdc.gov/niosh/topics/pesticides/pdfs/pest-sevindexv6.pdf
[5] Currently participating states are: California, Florida, Illinois, Louisiana, Michigan, Nebraska, New Mexico, North Carolina, Oregon, Texas and Washington. The participating states for a given year vary depending on state and federal funding for pesticide surveillance.

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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 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, 2016 to August 14, 2019, three human incidents involving flumethrin were reported to NPIC. One incidents was classified as inconsistent with flumethrin exposure and one incident was asymptomatic. These incidents were not further reviewed. The third incident was classified as minor severity. This incident involved a 74-year-old male that was exposed to the collar when a dog that was staying with him got into his bed. The following night he broke out in hives and was itching uncontrollably. He went to the ER and was treated with prednisone. He went home for 24-48 hours, had the same reaction, and went to the ER a second time. After the collar was removed from the dog he had no further symptoms. His wife (age unknown) was also sleeping in the bed and she had no symptoms.

d. Agricultural Health Study (AHS)

The AHS is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA. The AHS participant cohort includes more than 89,000 licensed commercial and private pesticide applicators and their spouses from Iowa and North Carolina. Enrollment occurred from 1993 – 1997, and data collection is ongoing. The AHS maintains a list of publications resulting from AHS studies[6]. If there are AHS findings in the published literature relevant to a pesticide undergoing registration review, the Agency will ensure these findings are considered in the problem formulation/scoping phase of the registration review process and, if appropriate, fully reviewed in the risk assessment phase of the process. Flumethrin is not included in the AHS, and therefore this study does not provide information for this report.

[6] Agricultural Health Study: Publications https://aghealth.nih.gov/news/publications.html

IV. CONCLUSION

Flumethrin is the active ingredient in only one end use product (Seresto Collar, Registration No. 11556-155) that was registered on March 16, 2012. This product is a pet collar used on dogs and cats to control fleas and ticks. It contains the active ingredients flumethrin and imidacloprid.

IDS, SENSOR-Pesticides, and NPIC databases were queried for flumethrin incidents. There were 252 flumethrin incidents reported to Main IDS and 374 flumethrin incidents reported to Aggregate IDS from January 1, 2016 to August 27, 2019. Nineteen of these incidents were classified a major severity, 233 incidents were classified as moderate severity and 374 were classified as minor severity. There were three low severity flumethrin incidents reported to SENSOR-Pesticide (2013-2015) and three incidents were reported to NPIC (2016-2019).

The total number of flumethrin incidents reported to IDS, from 2013 to 2018, appears to be increasing over time.

The Agency will continue to monitor the incident data and if a concern is triggered, additional analysis will be conducted.

Appendix A.

Major Severity Flumethrin Incidents Reported to Main IDS from 1/1/16 to 8/27/19				
Incident Package Report	**Incident Date**	**Location**	**Product Name**	**Incident Description**
029467 - 00005	6/27/2016	SYRACUSE, NE	SERESTO LARGE DOG	An adult male was exposed to a Seresto Large Dog Collar after the collar was applied to his dog. No direct product exposure was known. Immediately after petting the dog, he developed an erythematous rash on his arms. The rash resolved a week after the collar was removed from the dog.
029467 - 00007	2/1/2016	GA	SERESTO CAT	An adult female was exposed to a Seresto Cat collar when she applied it to her cat. At an unknown date (during the same month) post exposure, she experienced numbness and pain in her arms and legs. She was diagnosed with an unspecified inflammatory neurological disease.
029467 - 00009	8/1/2016	ARKADELPHIA, AR	SERESTO LARGE DOG	A 50-year-old female was exposed to a Seresto Large Dog collar when it was placed around the neck of her dog. On an unknown date post administration, her neck tingled and turned red after she hugged her dog. The symptoms resolved after she washed her neck. The cycle of symptoms and resolution continued every time she hugged the dog.
029516 - 00002	5/1/2016		SERESTO SMALL DOG	A 74-year-old female was exposed to a Seresto Small Dog collar when she placed around her dog's neck. Six months after application of the collar, she was examined by a physician who determined she had an unspecified interstitial lung disease.
029685 - 00005	6/27/2016		SERESTO LARGE DOG	An adult female was exposed to one Seresto Large dog collar after the collar was applied to her dog and she pet the dog. No direct product exposure with the collar was known. Immediately after petting the dog, she developed an erythematous rash on her arms. Three months later, the collar was removed. Approximately a week later, her rash resolved.
029959 - 00008	10/1/2016	PEPPERELL, MA	SERESTO LARGE DOG	A 73-year-old female was exposed to a Seresto Large Dog collar on her hands when she placed it on her dog. Six month later, she experienced skin lesions inside of her nose. Three months later, she removed the collar from the dog and the clinical sign continued but improved.
030085 - 00006	10/1/2016	BEAVER FALLS, PA	SERESTO LARGE DOG	A 37-year-old male was exposed to an unknown amount of 1 Seresto Large Dog caller when he mouthed his dog that had the collar applied on the same day. No known direct exposure to the collar. Immediately post exposure, he experienced intermittent numbing sensation on his tongue. He continued to mouth his dog and the sign continued intermittently. He removed the collar from the dog and recovered.
030303 - 00020	5/27/2017	TUNKHANNOCK, PA	SERESTO	A 58-year-old woman was exposed to 1 Seresto Cat collar and 1 Seresto large dog collar when her boyfriend applied them to the pets. Approximately one month later, she experienced ocular pain, ocular redness, blurred vision and eyelid edema. She was examined by an ocular physician who determined there was an eye infection.

030314 - 00004	5/1/2017	CHESTER, IL	SERESTO SMALL DOG	A 43-year-old male was exposed to 8 collars on his hands when he applied then to the dogs in his home. He was also exposed to the collars when four of the dogs slept in his bed each night. Approximately one-week post exposure, he developed nasal congestion, a bleeding skin lesion on his ear, ear drainage, a nasal irritation, and a throat irritation. He was examined by a physician who determined that he had a hole in the ear drum and started medication. He also removed the 8 dog collars from his dogs. The ear drainage resolved. He replaced the 8 dog collars and approximately 10 days later, his ear drainage returned.
030475 - 00002	1/1/2016	EASTLAKE, OH	SERESTO DOG (UNSPECIFIED)	An 83-year-old male was exposed to multiple Seresto Dog collars that were worn by his neighbor's dogs when he played with and pet them. An unspecified date post exposure, he developed a pruritic rash on his hands, arms, back and legs.
030589 - 00001	4/30/2017	FLEETWOOD, PA	SERESTO LARGE DOG	An adult female was exposed to two Seresto Large Dog collars when she nuzzled her dogs face to face. She developed a rash on her chin and lower eye lids. Three months later, she replaced her dogs' collars with new Seresto collars and approximately four hour later, the clinical signs worsened.
030942 - 00006	12/25/2017	IA	SERESTO (UNSPECIFIED)	A 34-year-old male was secondarily exposed to the collar when he was in the home of his parent's dog who was wearing the collar around its neck. Approximately four hours post exposure, he experienced generalized pruritus and hives on both arms. When he left the dog's residence, the clinical signs improved but continued.
031139 - 00010	6/1/2016	LILLIAN, AL	SERESTO (UNSPECIFIED)	An 84-year-old female was exposed to multiple collars when she applied them to her dog and 9 cats without wearing gloves. Sometime after exposure, she experienced a tingling sensation in her entire body, the sensation of the right side of the body being asleep and difficulty using the right arm and right hand.
031139 - 00012	5/1/2017	PLYMOUTH, MA	SERESTO DOG (UNSPECIFIED)	A 78-year-old male with asthma and allergies was exposed to a Seresto dog collar when his dog would rest against his neck. He had a tick removed from his neck and experienced a lesion and localized pruritus. The next month he experienced a lesion under his arm and localized pruritus. He was tested for Lyme disease and other tick-borne illnesses and the results were negative.
031139 - 00014	10/1/2017	ALVERTON, PA	SERESTO DOG (UNSPECIFIED)	An 80-year-old female to one dog collar. She developed a digestive tract disorder.
031139 - 00015	5/2/2018	BARNEVELD, WI	SERESTO LARGE DOG	A 67-year-old woman was exposed to 1 Seresto Large Dog collar when should would pet the dog and slept in the same bed as the dog after the collar was applied. Two days later, she experienced fatigue and heart flutter (arrhythmia).
032334 - 00009	2/15/2019	OLIVER SPRINGS, TN	SERESTO DOG (UNSPECIFIED)	On 14-Feb-2019, a 12-year-old, 130-pound boy in unknown condition, with the concomitant medical conditions of a digestive tract disorder NOS and elevated blood pressure. that was taking 15 mg of Lisinopril by mouth daily since an unknown date in 2019, was secondarily exposed to an unknown amount of a Seresto Dog (unspecified) collar that was worn by the dog in the home since approximately 14-Feb-2019, and the dog slept in the bed with the boy. It was unknown if direct contact with the collar occurred. On approximately, 15-Feb-2019, the boy experienced intermittent grand mal seizures, 1 episode of emesis that resolved approximately 5 minutes post onset and mental impairment. A toxicology blood screening

				panel and other unspecified blood panel were performed and were both within normal limits. The boy continued to have intermittent seizures and was examined by a pediatrician on emergency. Magnetic Resonance Imaging testing was performed of the brain with the results within normal limits. Approximately 12 hours post onset, the boy recovered. It was unknown if treatments were performed. The boy remained hospitalized for observation. On 19-Feb-2019, the boy was released from the hospital. On 26-J un-2019, the boy had a follow up exam performed with a pediatric neurologist. An electroencephalogram was performed and showed normal brain activity .
030787 - 00003	5/1/2017	TUCKERTON, NJ	SERESTO LARGE DOG	In approximately May 2017, an adult female was exposed to a Seresto Large Dog collar when she placed it on her dog. Sometime after that in May 2017, the she exhibited an unspecified eye disorder. She was examined by 5 different physicians and an allergy specialist. It was determined that she had an allergy. No known treatments were provided and the clinical signs continued. In Dec 2017, the individual removed the collar from the dog. The clinical signs continued.
030787 - 00006	6/1/2017	HARRISBURG, PA	SERESTO DOG (UNSPECIFIED)	A 68 year old female with concomitant medical conditions of arthritis, osteoarthritis of the hand, carpal tunnel syndrome, a chronic renal disorder NOS, bile duct disorder NOS, gastric esophageal reflux disease (gastric irritation), heartburn, hypothyroidism, hypertension, osteoporosis (bone and joint disorder NOS), atrial fibrillation, pancreatic lesion (pancreas disorder), stenosing tenosynovitis/trigger finger (tendon injury), vitamin D deficiency, Fuchs corneal dystrophy (eye disorder NOS), corneal ulcer (corneal disorder NOS), diplopia esotropia (diplopia). posterior capsule opacification (eye disorder NOS), peripheral vascular disorder, anterior basement membrane dystrophy (eye disorder NOS) and abducens (6th) nerve palsy (cranial nerve disorder), was exposed to 1 Seresto Large Dog collar while the dog slept with her each night. Sometime post exposure she experienced double vision. She was examined by multiple physicians (neurologist, primary care physician, prism eye doctor and a general eye doctor) and had multiple tests performed (MRI, fluorescein, various ocular tests, CT scan and bloodwork). No abnormalities were found. In June 2017, the individual experienced headaches and one eye was unable to move (eye disorder NOS). She was examined by a physician, hospitalized for 3 days, and administered an unspecified dose of intravenous fluids. It was determined by physicians that the woman had an unspecified nerve palsy (cranial nerve disorder). Sometime after that she removed the collar from the dog. Sometime later she replaced the collar on her dog and her clinical signs worsened.

Appendix B.

Flumethrin Incidents Reported SENSOR-Pesticide from 2013-2015			
Year	**State**	**Severity**	**Incident Description**
2013	North Carolina	Low	An adult woman was exposed to the collar when it was applied to her dog. She experienced a rash.
Not Available	New York	Low	The case was exposed to the collar when she 1) slept with dogs while the dogs were wearing their collar, 2) exposed to collar while trying to restrain dogs, and 3) placed collar on her bare skin (stomach). She experienced rhinitis, urticaria, pruritus, erythema, eye irritation, conjunctivitis, nasal irritation and nasal discharge, and ocular irritation
2013	New York	Low	A veterinarian applied the collar to the case's dog. The collar accidentally broke open on the case's hands. She experienced nausea, blurred vision, and heart palpitations

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