Flea and Tick “Spot-On Medicines” are not Considered Drugs or Regulated as Such and may be Harmful to Your Pet’s Health

Tag Words: Flea and Tick spot-on products, pesticides, EPA, harmful products

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Summary: Rising concerns of the toxicity of Flea and Tick products for companion animals was triggered by an influx of incident reports of adverse effects from these preventatives. In April 2009, the Environmental Protection Agency distributed an advisory concerning approximately 70 spot-on flea and tick control products due to an increase in the number of reports of adverse reactions to the products. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) gives the EPA the responsibility for ensuring that pesticides sold in the U.S. do not cause harm to animal health when used properly. Although spot-ons may seem to be considered "drugs," they are mostly regulated by the EPA because these products are actually considered to be pesticides. Although some Flea and Tick products have been deemed inactive by the EPA, some of them are still currently available in stores. As of February 2013, Sergeant’s Gold Squeeze on for Dogs, which contains 40% cyphenothrin and 2% pyriproxyfen, is now listed as being “inactive.” Both Promeris Spot On for Cats and Dogs were inactivated by the EPA on September 28, 2011. Although these products are no longer being manufactured, we have experienced an adverse effect first-hand from Sergeant’s product EPA Reg. No. 2517-80. Since there are no requirements that the spot-on products containing pesticides be tested on dogs or cats, there is not guarantee that these products will not harm your pet. Many consumers are uninformed of the hazardous effects of these products, and it is the responsibility of the EPA as well as the pet care companies that are manufacturing these products to increase awareness and conduct better pre-market clinical trials and post market surveillance.

Video Link: http://www.youtube.com/watch?v=BsyY3o8-d9e

Pets sickened by a Flea and Tick Spot-On Product
It was the first hand experience by one of the authors of this paper that prompted investigation of these products. The pet owner had purchased from Acme Markets in PA Sergeant’s Gold flea and tick squeeze-on for dogs that had a “new formula with skin protection technology P002653-1”. The product purchased was for dogs between 40-60 lbs. One could also purchase a product with the same name but for different weight dogs. In May 2013, the pet owner, wearing latex gloves, applied the product as described on the packaging to her 48 lb long-haired purebred dog. After cutting one of the 0.15 fl oz tubes, the dogs hair was parted on the back between the shoulder blades and the contents of the tube was squeezed out onto the skin in that area. On application, it was clear that the dog felt something uncomfortable being applied. Immediately following, the dog lied down and tried to bite and scratch with her foot the area unsuccessfully (the dog couldn’t reach the area where it was applied). That day and several days following, the dog paced incessantly - like she didn’t know what to do with herself. It was when the vomiting started, as did an uncontrollable diarrhea on the home’s white carpeting, that prompted the pet owner to look on the back of the packaging and call the number that was supplied. A person
named Wayne answered and the pet owner described what the dog was experiencing. He said that it was likely an “allergic reaction” and that “the area” should be washed with Dawn or Palmolive. He said that the “drug” “just” stays on the skin and hair and protects the dog from fleas and ticks by the product being in the natural oils of the skin. The pet owner replied that the product must be inside the dog’s body to cause vomiting and diarrhea. Wayne said that that was likely just (again just) an allergic reaction and that it didn’t “go systemic”. He then said “thank you, and was there anything else he could help with”, the premise to hanging up.

Outraged (which may be a little too strong a word here), the pet owner asked why he hadn’t asked what exactly the product was that had sickened the dog, or taken my name. Clearly, without that information, he would not be able to file an incident report. The pet owner then requested that he take the pet owner’s name and the product number and that he file some sort of product complaint.

The pet owner took the dog to have a bath and the dog appeared to have recovered - but who knows - was there any permanent damage to the liver or other organ that may go unseen for a time? Several weeks later, the pet owner received a get well card in the mail and under separate cover, a form to fill out...More on that form...

**Rising Concerns of the Toxicity of Flea and Tick Spot On Treatments**

In April 2009, the Environmental Protection Agency distributed an advisory concerning approximately 70 spot-on flea and tick control products due to an increase in the number of reports of adverse reactions to the products. Adverse effects included in the reports consisted of skin irritation, skin burns, seizures, and death. When reviewing reports of adverse events, the EPA found that from 2007 to 2008, the numbers of adverse event incidents increased by 53%. A total of approximately 43,000 incidents were reported for 2008. Products containing the active ingredients cyphenothrin, pyriproxyfen, phenothrin, S-methoprene, permethrin, dinotefuran, imidacloprid, amitraz, metaflumizone, fipronil, and etofenprox were involved in the analysis. The EPA met with the manufacturers of the products to discuss the issue in May 2009. In a July 2009 advisory, the EPA and the Food and Drug Administration notified consumers to be wary when using these products and to consult with their veterinarian.

**Measures implemented by the EPA to promote product safety**

The EPA announced it was taking steps to increase the safety of spot-on pesticide products for flea and tick control for cats and dogs on March 17, 2010. These steps include changing product labels to deter misuse and to ensure appropriate weight ranges for products, increased pre-approval safety testing and post market surveillance, conditional product registrations with time limitations, and standardized sales and adverse events reporting. Currently there are no pre-market clinical trials that are required for EPA approval. Emulating the FDA Center for Veterinary Medicine, the EPA plans to implement tighter regulations associated with spot-on products in general, including standardized adverse event reporting data and sales report data, and equivalent standards to those used by the CVM in approving and reviewing animal drugs. The EPA will take steps to bring data requirements more in line with the FDA's testing requirements to allow the EPA to more thoroughly assess the safety of the products.
When is it mandatory to recall Flea and Tick Products?
There isn't a specific number or maximum level of adverse events that is acceptable. The EPA reviews the reports and considers each product on a case-by-case basis. In addition, any significant increase in the number of adverse events reported for a product will trigger a thorough review of the product and the reports. The EPA also does not have legal authority to regulate where spot-on products are sold or who sells them.

Who regulates Flea and Tick Treatments?
The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) gives the EPA the responsibility for ensuring that pesticides sold in the U.S. do not cause harm to animal health when used properly. Although spot-ons may seem to be considered "drugs," they are mostly regulated by the EPA because the parasites they control, such as fleas, ticks and, mosquitoes, lice and mites, are considered pests, and these products are actually considered to be pesticides. The federal law requires EPA registration of pesticides before they can be sold to the public. Some spot-on products are actually considered animal drugs and are instead regulated by the FDA. Very few spot-ons are regulated by the Food and Drug Administration as prescription drugs. As a general rule, spot-ons that only treat external parasites are regulated by the EPA while spot-ons that treat external parasites AND internal parasites, such as intestinal worms, are considered animal drugs and are regulated by the FDA. Flea and tick products that are given orally or by injection are regulated by the FDA. The FDA approval process involves submission of specific drug information to the FDA’s Center for Veterinary Medicine (CVM). The new animal drug application (NADA) requires submission of important background information for the drug including chemical composition, manufacturing processes, and labeling specifics. The NADA also requires a freedom of Information (FOI), which summarizes the efficacy and target animal safety data.

To determine if a particular flea and tick treatment is regulated by the EPA or the FDA, the consumer should look on the label. If the product is regulated by the EPA, the label includes the EPA Reg. No. Products that are regulated by the FDA have a New Animal Drug Application number which can usually be found on the product's label and package insert, along with the statement "Approved by FDA."

How does the EPA Regulate Flea and Tick Treatments?
Before a manufacturer can sell or distribute any pesticide in the U.S., the EPA must review the data from studies on the pesticide to determine that its use will not pose unreasonable risks to human health, to the environment, or to non-target species. The EPA's Guideline No. 870.7200, "Companion Animal Safety" lists pre-market testing requirements for pesticide products to be used in dogs and cats. Safety of up to 5 times the labeled dosage must be demonstrated. Once it has been determined that the product does not pose unreasonable risks, it is licensed or registered for use only according to the label directions.

Once a product is registered with the EPA, it must have a registration review every 15 years, unless the EPA cancels the registration. Because it can be more difficult to retract a registration once a product is approved and on the market, the EPA is also considering conditional registration. A conditional registration would have time limitations and more strict conditions placed on the registration, which would allow the EPA more freedom to evaluate the products' safety data.
safety on a regular basis. For a product that is conditionally registered, the EPA can re-evaluate the product’s safety, when the approval is due to expire, to determine whether or not they would renew the registration.

Before allowing the use of a pesticide on food crops, EPA sets a tolerance, or maximum residue limit, which is the amount of pesticide residue allowed to remain in or on each treated food commodity. The tolerance is the residue level that triggers enforcement actions. That is, if residues are found above that level, the commodity will be subject to seizure by the government. In setting the tolerance, EPA must make a safety finding that the pesticide can be used with "reasonable certainty of no harm." To make this finding, EPA considers

- the toxicity of the pesticide and its break-down products
- how much of the pesticide is applied and how often
- how much of the pesticide residue remains in or on food by the time it is marketed and prepared

Process of assessing the possible risks of pesticides

Step 1 Hazard Identification: The first step in the risk assessment process is to identify potential health effects that may occur from different types of pesticide exposure. EPA considers the full spectrum of a pesticide’s potential health effects. For human health risk assessments, many toxicity studies are conducted on animals by pesticide companies in independent laboratories and evaluated for acceptability by EPA scientists. EPA evaluates pesticides for a wide range of adverse effects, from eye and skin irritation to cancer and birth defects in laboratory animals. EPA may also consult the public literature or other sources of supporting information on any aspect of the chemical.

Step 2 Dose Response Assessment: the amount of a substance a person is exposed to is as important as how toxic the chemical might be. For example, small doses of aspirin can be beneficial to people, but at very high doses, this common medicine can be deadly. In some individuals, even at very low doses, aspirin may be deadly. Dose-response assessment involves considering the dose levels at which adverse effects were observed in test animals, and using these dose levels to calculate an equal dose in humans.

Step 3 Exposure Assessment: People can be exposed to pesticides in three ways:

1. Inhaling pesticides
2. Absorbing pesticides through the skin
3. Oral exposure of pesticides or digestive tract

Step 4 Risk Characterization: Risk characterization is the final step in assessing human health risks from pesticides. It is the process of combining the hazard, dose-response and exposure assessments to describe the overall risk from a pesticide. It explains the assumptions used in assessing exposure as well as the uncertainties that are built into the dose-response assessment. The strength of the overall database is considered, and broad conclusions are made. EPA’s role is to evaluate both toxicity and exposure and to determine the risk associated with use of the pesticide.
Risk = Toxicity x Exposure

The risk to human health from pesticide exposure depends on both the toxicity of the pesticide and the chance that a person comes into contact with it. If the pesticide is very poisonous, but no one is exposed, there is no risk. Likewise, if there is ample exposure but the chemical is non-toxic, there is no risk. The EPA recognizes that effects vary between animals of different species and from person to person. To account for this variability, uncertainty factors are accounted for in the risk assessment. These uncertainty factors create an additional margin of safety for protecting people who may be exposed to the pesticides. FQPA requires EPA to use an extra 10-fold safety factor to protect infants and children from effects of the pesticide.

**Chemical Review Managers**

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<td>Cyphenothrin</td>
<td>K. avivah jakob</td>
<td><a href="mailto:jakob.kathryn@epa.gov">jakob.kathryn@epa.gov</a></td>
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<td>703-305-7106</td>
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<td>John Hebert</td>
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**Toxicity tests required by the EPA for pesticide approval**
EPA evaluates studies conducted over different periods of time and that measure specific types of effects. These tests are evaluated to screen for potential health effects in infants, children and adults.

**Acute Testing**: Short-term exposure; a single exposure (dose).
- Oral, dermal, and inhalation exposure
- Eye irritation
- Skin irritation
- Skin sensitization
- Neurotoxicity

**Sub-chronic Testing**: Intermediate exposure; repeated exposure over a longer period of time usually 30-90 days.
- Oral, dermal, and inhalation
- Neurotoxicity (nerve system damage)

*Chronic Toxicity Testing*: Long-term exposure; repeated exposure lasting for most of the test animal's life span, which is intended to determine the effects of a pesticide after prolonged and repeated exposures.
- Chronic effects (non-cancer)
- Carcinogenicity (cancer)

*Developmental and Reproductive Testing*: Identify effects in the fetus of an exposed pregnant female and to determine how pesticide exposure affects the ability of a test animal to successfully reproduce.

*Mutagenicity Testing*: To assess a pesticide's potential to affect the cell's genetic components.

*Hormone Disruption*: To measure effects for a pesticide’s potential to disrupt the endocrine system. The endocrine system consists of a set of glands and the hormones they produce that help guide the development, growth, reproduction, and behavior of animals including humans.

**For more information regarding pesticide approval**

Information on EPA's pesticide regulatory program and a variety of pesticide-related publications, such as the fact sheets on registration and risk assessment, are available from the Office of Pesticide Programs, Communication Services Branch, Ariel Rios Building, 1200 Pennsylvania Ave. NW, Washington, D.C. 20460. Or call us at 703-305-5017.

The EPA Office of Pesticide Programs’ home page contains further information on EPA's pesticide regulatory program, including fact sheets on various topics. Periodic updates on new registrations and tolerances as well as progress in implementing the tolerance reassessment schedule and other provisions of the Food Quality Protection Act (FQPA) also will be published at this Internet site.

Information on pesticides and their toxicity is available from the National Pesticide Information Center at 1-800-858-7378.

**Drug Approval Process**

The Federal Food, Drug, and Cosmetic Act gives the U.S. Food and Drug Administration (FDA) the legal authority to approve and regulate drugs for both people and animals. If a drug is for use in animals, it is called a new animal drug. New animal drugs are approved and regulated by the FDA’s Center for Veterinary Medicine (CVM). The CVM consists of six offices that work together to approve new animal drugs and monitor the drugs after they are on the market. The drug sponsor collects information about the safety and effectiveness of a new animal drug by conducting several studies. Based on the results from the trials, the sponsor decides if there is enough proof that the drug is safe and effective to meet the requirements for approval. The sponsor submits a New Animal Drug Application (NADA) to the CVM, which consists of veterinarians, animal scientists, biostatisticians, chemists, microbiologists, pharmacologists, and toxicologists to review the NADA. The drug sponsor can legally sell the animal drug if the CVM
team approves the NADA by agreeing with the sponsor’s conclusion that the drug is safe and effective if it is used according to the proposed label.

The drug sponsor initiates the animal drug approval process by contacting the Office of New Animal Drug Evaluation (ONADE) to open an Investigational New Animal Drug (INAD) file, discuss Animal Drug User Fee Act (ADUFA) fees, and discuss the development plan for the new animal drug. By opening an INAD file in the beginning of the drug approval process, the sponsor uses the file as a way to correspond with CVM throughout the process. Under the ADUFA of 2003, drug sponsors must pay CVM a “user fee” to review each NADA.

The drug sponsor must first figure out the dosage form of the drug and the dosage regimen that will be on the drug’s label. The dosage form is the drug’s physical form when it comes out of the manufacturing facility. There are several categories of dosage forms, including oral and injectable. Tablets and capsules are two types of an oral dosage form. A drug that is injected under the skin, into muscle, or into a vein is an injectable dosage form. The dosage routine includes the dosage of the drug, the frequency of taking the drug, the length of time or duration of taking the drug, and the route of administration. Possible routes of administration include injecting the drug under the skin, into muscle, or into a vein, giving the drug by mouth, or applying the drug topically to the skin.

The five parameters to consider when approving a New Animal Drug include:

- Target Animal Safety
- Effectiveness
- Human Food Safety
- Chemistry, Manufacturing, and Controls; and
- Environmental Impact

**Target Animal Safety**

The drug sponsor must show that the drug is safe to the target animal species when it is used according to the label. To prove the drug’s safety, sponsors typically conduct a target animal safety study in a small number of healthy animals. The two goals of a standard target animal safety study are to identify any possible adverse effects of the drug and to establish a margin of safety for the drug. The margin of safety is usually determined by testing the drug at higher-than-labeled doses for a longer-than-labeled time period in the target animal species. The drug’s margin of safety is like a “cushion” to make sure the drug will be safe when it is used in animals that may be sensitive to the drug. During clinical trials of the animal drug, safety information is collected by examining the animals, observing their behavior, looking at their bloodwork results, an observing their tissues and organs both with the naked eye and under a microscope.

**Effectiveness**

The drug sponsor must show that the drug is effective in the target animal species when it is used according to the label. One way for sponsors to prove the drug’s effectiveness is by conducting a field study. In a field study, all the animals in the study have the disease or condition that the drug will be used for. For example, if the drug will be used to treat urinary tract infections (UTIs) in dogs, a dog must have a UTI to be in the field study. The goal of the field study is to
make sure the drug will do what it is supposed to do when it is used under normal conditions and according to the label.

**Human Food Safety**
Food products made from treated animals must be tested to ensure that the animals are safe for people to eat. To show that the food products are safe, a drug sponsor usually conducts what are called human food safety studies. Chemical residues of the drug may be present in or on food products made from the animal that has been treated with an animal drug. Chemical residues include small amounts of leftover drug, or parts of the drug that are not completely broken down by the animal’s body. One goal of the human food safety studies is to make sure the level of chemical residues in or on food made from treated animals will not harm people.

**Chemistry, Manufacturing, and Controls**
In the Chemistry, Manufacturing, and Controls (CMC) technical section, the drug sponsor describes the plan for making the drug. This plan includes the active ingredients that will be used to make the drug, where the ingredients will be derived from, where the drug will be created, how the drug will be created, how the drug will be packaged, the conditions and method for storing the drug, and the length of time a drug can be stored before it expires. Investigators from the FDA often work with scientists at CVM to ensure that the manufacturing facilities where a particular drug is made has the correct equipment and methods to consistently produce a high-quality and safe drug.

**Environmental Impact**
Under the National Environmental Policy Act (NEPA), CVM must consider how the environment will be affected by an animal drug after it is approved. The CVM requires that drug sponsors prepare an Environmental Assessment (EA), which describes how much drug is expected to get into the environment and its potential effects on the environment. If CVM decides that the drug will not have a significant impact on the environment based on the information in the EA, CVM writes what is called a Finding of No Significant Impact (FONSI). If CVM decides that the drug will have a significant environmental impact, CVM writes an Environmental Impact Statement (EIS). A drug sponsor may ask the CVM for a waiver, called a categorical exclusion (CE), to avoid having to prepare an EA. A CE means that the drug falls into a legally-defined category that is unlikely to cause a significant environmental impact. The CVM typically grants a CE when considering a drug for companion animals, such as cats and dogs. A drug used for companion animals is not likely to get into the environment because it is administered to one animal at a time, rather than to a herd or flock of animals.

**Labeling**
The term “labeling” includes all the information on the immediate container, package insert, outer packaging, shipping label, and client information sheet. In the Labeling technical section, CVM looks at the complete labeling in its final form. CVM makes sure the labeling provides all the necessary information to use the drug safely and effectively, including the risks associated with the drug. CVM also makes sure the labeling is not false or misleading.
The Freedom of Information (FOI) Summary is a public document that summarizes the safety and effectiveness information submitted by the sponsor to support the approval of an original or supplemental NADA and forms the basis for the agency's approval of an NADA. This information is released by the Food and Drug Administration (FDA) when the approval is published in the Federal Register in accordance with 21 CFR section 514.1(e). The purpose of the FOI Summary is to inform the public by providing the basis on which the Agency approved the NADA or supplement. Summaries are provided for pivotal and supplementary studies supporting safety and effectiveness of the drug in the target animal as well as human food safety. The FOI Summary includes general information about the approved drug, indications for use, dosage form and route of administration, explanation of the recommended dosage, and the FDA’s conclusion. A Freedom of Information Act request can be written in order to obtain a copy of an FOI Summary that is not electronically available.

Electronic copies of the FOI Summaries for approved animal drugs can be accessed at: http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.

If an electronic copy of the FOI Summary is not available online, a hardcopy can be requested in writing. Information on how to make a written request to CVM for an FOI Summary can be accessed at: http://www.fda.gov/RegulatoryInformation/FOI/HowtoMakeaFOIAResquest/default.htm.

After the FDA approves the New Animal Drug
After the drug is approved, a notice of approval is published in the FEDERAL REGISTER, and the drug sponsor can legally sell the drug. Despite if the drug is a brand name animal drug or a generic copy, the CVM’s stamp of approval stands for safety and effectiveness when the drug is used according to the label. The extensiveness of the drug approval process protects the health of both animals and people by assuring that only safe, effective, and high-quality animal drugs make it to the market, while unsafe animal drugs and those that do not work are kept off.

Flea and Tick Drugs Regulated by the FDA
PROGRAM Flavor Tabs (NADA 141-035) and CAPSTAR Tablets (NADA 141-175) are oral tablets provided by Novartis. The generic names for PROGRAM Flavor Tabs and CASPSTAR Tablets are lufenuron and nitenpyram, respectively. PROGRAM Flavor Tabs are available in four tablet sizes according to the weight of the dog and cat. Each tablet size is available in color-coded packages of six tablets each. CAPSTAR Tablets are available in two tablet sizes according to the weight of the dog and cat. Each tablet size is available in color-coded packages of six tablets each. The available doses of PROGRAM Flavor Tabs are 45 mg, 90 mg, 204.9 mg and 409.8 mg and the doses for CAPSTAR Tablets are 11.4 mg and 57 mg. Before the CAPSTAR was approved, several studies were conducted. As a part of the effectiveness studies for cats and dogs, dosage characterization, dosage confirmation, clinical field study, bioequivalence study. PROGRAM was approved on January 23, 1997. The drug has several patent numbers, including 5,416,102 and 5,420,163, which expire May 30, 2012, 4, 798, 837, which expired January 31, 2006, and 5,153,224, which expired October 6, 2009. The FDA concluded from the studies that the data in support of the supplemental NADA (New Animal Drug Application) satisfied the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514.
of the implementing regulations. The data demonstrated that CAPSTAR Tablets, when administered in accordance with the directions provided by the revised labeling, are safe and effective for the treatment of flea infestations on dogs, puppies, cats, and kittens. Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, the approval qualifies for three years of marketing exclusivity beginning on the date of the approval. CAPSTAR was approved June 11, 2003 and is under the following U.S. patent number 5,750,548, which expires April 29, 2016.

Who to Contact in the Event of an Adverse Reaction
According to the EPA’s website, the companies that manufacture the products are required by law to report incident information to the EPA. Contact information can be found on the product label. Consumers should clearly identify the name of the product used, the EPA Registration Number, the type and breed of animal affected, symptoms observed in the pet, and any other details pertaining to the incident. If a pet shows any unusual reaction soon after application, consumers should immediately remove any remaining product from the pet by bathing the pet in mild soap and rinse with large amounts of water, unless the product specifically states not to or doing so would be stressful for the animal. Unusual reactions may include neurological symptoms such as distress, nervousness, tremors, and signs of skin irritation. In addition, you should immediately consult with your veterinarian.

Pet owners should always report adverse effects to the product registrant. The following criteria are necessary for a thorough incident report.

1. Name(s) and EPA registration number(s) of product(s) applied
2. Active ingredient of the product (if known; can be found on the product label)
3. Breed(s) and age(s) of animal(s) and any other factors needed to understand any previous medical condition(s) of animal(s)
4. Who applied the product(s)-owner or veterinarian
5. Length of time between application and reaction
6. Description of adverse reaction
7. Date(s) on which adverse reaction occurred
8. Contact information and telephone number
9. City and State where the incident occurred

EPA’s Pesticide Program is responsible for regulating pesticide products in the United States and ensuring that they can perform their intended functions without posing risks to humans, animals, or the environment. All incident information will be forwarded to the EPA’s database manager for inclusion in the EPA Pesticide Incident Data System, which contains information from reported pesticide poisonings. EPA routinely examines information from this database to determine what concerns are being raised about registered products and whether further regulatory action is needed.

Pet owners should also remember to report adverse effects to the product registrant, which is required by law to report it to EPA. Contact information can be found on the product label. Clearly identify the name of the product used, the EPA Registration Number, the type and breed
of animal affected, symptoms observed in the pet, and any other details pertaining to the incident.

Veterinarians have access to a reporting mechanism called the Veterinary Pesticide Adverse Effects Reporting portal at http://npic.orst.edu/vet to report incidents. This portal is not for use by the public. Consumers may also contact the National Pesticide Information Center at 800-858-7378 to report an incident.

The ASPCA Animal Poison Control Center (888.426.4435) can also provide emergency guidance for pet owners and veterinarians. The center usually charges a fee for consultation.

Tell the National Pesticide Information Center: Call 1-800-858-7378 to report an incident. Section 6(a)(2) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) requires pesticide product registrants to submit adverse effects information about their products to the EPA. Registrants’ 6(a)(2) submissions through the U.S. mail must be mailed to the following address:

Document Processing Desk -6(a)(2)
Office of Pesticide Programs- 7504P
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

Registrants' 6(a)(2) submissions via courier service must be addressed as follows:
For all deliveries, see "Visiting the Office of Pesticide Programs" for office location and building access information

Document Processing Desk - 6(a)(2)
Office of Pesticide Programs
Document Processing Room S-4900
One Potomac Yard
2777 S. Crystal Drive
Arlington, VA 22202

Conflict of interest?
Is self-reporting a negative experience with a product to a regulatory agency, which is “required”, something that will be done? Is it like the fox guarding the chicken house? In the author’s experience, the Sergeant’s employee had no intention of filing an incident report until the pet owner pursued it further. The pet owner may also decide to call their veterinarian. It is unlikely that the veterinarian’s office would offer any advice without seeing the patient first. Given that the vet would charge for an office visit, some pet owners may opt not to call or report the incident to the veterinarian or seek their medical advice.
The detrimental impact of Sergeant’s active ingredient Cyphenothrin
There have been many reports of dogs experiencing adverse effects from Sergeant’s Gold Flea and Tick medicine than any other brand. The active ingredient in Sergeant’s Gold Flea and Tick Squeeze-On for Dogs is cyphenothrin (Gokilaht), which is exclusive to Sergeant’s, as well as pyriproxyfen (Nylar), an insect growth regulator that kills flea eggs and larvae. According to the EPA’s report on topical adverse effect by active ingredient in 2008, Cyphenothrin accounted for 22,880 of the total adverse effects. Cyphenothrin is a synthetic chemical derived from natural chemicals found in chrysanthemums. As a pyrethroid, cyphenothrin can cause allergic responses and potentially disrupt the endocrine system. Being an active ingredient in Sergeant’s Flea and Tick Squeeze-On for Dogs, it is suspected that cyphenothrin is responsible for the numerous reports of adverse effects experienced by dogs who have been administered this medication.

As of February 2013, Sergeant’s Gold that contained 40% cyphenothrin and 2% pyriproxyfen is now listed as being “inactive”; i.e. taken off the market. Inactive means that it doesn't do anything or doesn't affect the desired outcome (flea+ tick preventive). So-, being somewhat facetious, should the word "inactive" also have as a definition in a dictionary as "toxic", "hazardous to one’s health"?. One could argue that, depending on the sensitivity of individual dogs, 20% , such as can be found in Sentry’s product “active” on the market now with 20% Cyphenothrin (and 2% Pyriproxyfen) could be as harmful as 40%. Perhaps the proper thing to do would be to remove from the market all products to be used on animals containing this pesticide.

Removing the Flea and Tick product from the “Active” list to the “Inactive” list

When speaking with Dr. Adrian Enache, the direction of the EPA’s pesticides program in Region 2, he explained the two scenarios in which a product could be concluded to be “inactive.” The registrant, such as the company producing the product, could request inactivation of the product from the EPA. Reasons for requesting inactivation include economic reasons, marketing reasons, or the acquisition of information conveying that the product is no longer considered effective or safe. For the second scenario, the EPA could force cancellation of the product if, when analyzing new information, they reach the conclusion that the product is no longer deemed to be safe for use. In the event that the company requests inactivation from the EPA, the registrant has 18 months from the date of cancellation to stop manufacturing the product. If the EPA forces cancellation, the company is not allowed to manufacture or distribute the product beginning on the date of cancellation. However, the product can be used until the stock is exhausted. We have experienced an adverse reaction to Sergeant’s Flea and Tick spot-on treatment EPA Reg. No. 2517-80 because the company requested inactivation of the product, and thus the registrant has 18 months to exhaust their supply. The product was cancelled in February 2013; therefore, 18 months has not passed since the date of cancellation. Even past the date of cancellation, the company is not required to recall all of their products from the shelves unless the product poses an extremely serious problem that warrants immediate safety concern. Dr. Enache explained how DDT (dichlorodiphenyltrichloroethane), which is an organochlorine insecticide, was banned by the EPA and thus it is illegal for the manufactures to continue producing it. However, it is legal for farmers to continue to use it as long as it has not expired and is stored properly.

Dr. Adrian Enache can be reached at (732) 321-6769 or via email at enache.adrian@epa.gov
**Mechanism of action of cyphenothrin and pyriproxyfen**
Pyriproxyfen is a juvenile hormone analog that functions as an insecticide by overloading the hormonal system of the target insect. The molting hormone and the juvenile hormone (JH) are two major insect-hormones that act to control metamorphosis. High concentrations of JH and low concentrations of molting hormone cause molting larva to continue growing as larval instars. JH prevents the insect from becoming an adult before it is fully grown and abnormal amounts of JH often result in the eventual death of the larva.

**Products containing Metaflumizone have been found to cause much harm to pets**
The Department of Pesticide Regulation (DPR) registered two pesticide products containing metaflumizone, including Promeris for Cats, EPA Reg. No. 80490-3, and Promeris for Dogs, EPA Reg. No. 80490-2. The DPR conditionally registered Fort Dodge Animal Health’s product Promeris for Cats, containing 18.53% metaflumizone, on May 10, 2007. Promeris for Cats is labeled to control fleas on cats, and is available only from licensed veterinary professionals. The conditional registration was dependent upon submission of an acceptable one-year storage stability and corrosion characteristics study. Fort Dodge Animal Health submitted the requested data and DPR granted Promeris for Cats full registration on August 17, 2007. On August 20, 2007, DPR registered Fort Dodge Animal Health’s product Promeris for Dogs, which contains 14.34% metaflumizone and 14.34% amitraz. Promeris for Dogs is labeled for control of fleas, mites, and ticks on dogs and is also available only from licensed veterinary professionals. Both Promeris Spot On for Cats and Dogs were inactivated by the EPA on September 28, 2011. Based on data obtained from the EPA on April 1, 2012, there were 2820 incident reports for Promeris Spot On for Dogs and 256 reports for Promeris Spot On for Cats.

**Other popular flea and tick preventatives**
Other popular flea and tick preventatives include Frontline Plus for Dogs, which contain other compounds fipronil and the insect growth regulator (IGR) (S)-methoprene. In fleas, the mode of action of methoprene is similar to pyriproxyfen. S-methoprene is also an IGR and halts the growth of chitin, which comprises the exoskeleton of insects. Since mammals do not produce chitin, IGRs are non-toxic to humans.

**Active Ingredients of flea and tick preventatives**

**Pyrethroids**
- Cyphenothrin: CAS#39515-40-7
- Phenothrin: CAS#26002-80-2
- Permethrin: CAS# 52645-53-1
- Etofenprox: CAS# 80844-07-1

**Formamide**
- Amitraz: CAS#33089-61-1

**Insect Growth Regulators**
- Pyriproxyfen: CAS#95737-68-1
- Methoprene: CAS#40596-69-8

**Phenylpyrazole**
- Fipronil: CAS#120068-37-3

**Neonicotinoids**
Mechanism of action of the Active Ingredients in flea and tick preventatives

Pyrethroids

It is currently unknown to the EPA whether the pyrethroids as a class have similar effects on all nerve channels or whether modifications of different types would have cumulative effect. The Agency also does not have a clear understanding of the effects of pyrethroids on key downstream neuronal function or how these key events interact to produce their specific patterns of neurotoxicity. Lacking such understanding prevents the EPA from making common mechanism of toxicity finding. Therefore, EPA is not currently following a cumulative risk approach based on a common mechanism of toxicity for the pyrethroids. To appropriately identify a research group or subgroups for such an assessment, the Agency has determined further study is needed regarding the assumptions of dose additivity and common mechanisms of toxicity.

Cyphenothrin: CAS#39515-40-7 (Pyrethroid)

As an ectoparasiticide, Cyphenothrin is active only against external parasites such as flies, lice, mosquitoes, ticks and mites. As a pyrethroid pesticide, cyphenothrin can cause allergic responses and potentially disrupt the endocrine system. Pyrethroids are synthetic chemical insecticides that have a similar mode of action to that of pyrethrins and have chemical structures adapted from the chemical structures of pyrethrins. Derived from chrysanthemum flowers, which are most commonly found in Australia and Africa, Pyrethrins are botanical insecticides that cause paralysis in target insect pests. To enhance their pesticidal properties, most pyrethrins and some pyrethroid products are formulated with synergists, including piperonyl butoxide and MGK-264. The purpose of synergists is to enhance the effectiveness of other chemicals since they do not have pesticidal effects of their own. Through licking and grooming, treated animals can ingest cyphenothrin. The enzyme, glucuronidase enables the absorbed cyphenothrin to be metabolized in the liver to non-toxic metabolites, which are excreted through urine. Since cats lack this enzyme, they are unable to metabolize synthetic pyrethroids. As a result, cyphenothrin and other pyrethroids are very toxic to cats. Having a similar mode of action to organochlorines, synthetic pyrethroids act on the membrane of the nerve cells and essentially block the closure of the ion gates of the sodium channel during re-polarization. The transmission of nervous impulses is strongly disrupted as a result, and eventually causes death of the pest.

Phenothrin: CAS#26002-80-2 (Pyrethroid)

Phenothrin kills insects by direct contact and ingestion. D-Phenothrin is a type I pyrethroid that affects the insect's central and peripheral nervous system by preventing the closure of voltage-gated sodium channels open for prolonged periods of time, causing repetitive nerve discharge and increased excitation. Flea and tick products for cats and kittens containing phenothrin have been cancelled since 2005 in response to the number of incident reports the EPA received regarding cases of serious illness or deaths among cats and kittens resulting from the use of
phenothrin flea and tick products. In addition to the phenothrin reported incidents, the EPA also received, over the past ten years, a handful of reported incidents of apparent neurological symptoms and other various complications following phenothrin flea and tick treatment on dogs.

**Permethrin: CAS# 52645-53-1 (Pyrethroid)**
Permethrin is a broad spectrum non-systemic synthetic pyrethroid insecticide whose cis isomer is considerably more toxic than the trans isomer. It acts on the nervous system of insects by interfering with sodium channels to disrupt the axonic nerve impulse conduction. Delayed repolarization and paralysis of the pests are the consequences of this disturbance. It is highly toxic to honeybees, fish, and aquatic invertebrates. Mammals are less susceptible to these pesticides as compared to insects because their sodium channels are less sensitive to pyrethroids and recover more rapidly. Due to their large body size, mammals are able to metabolize pyrethroids more quickly and prevent them from affecting the nervous system. However, cats can be sensitive to products with high concentrations of Permethrin due to insufficient glucoronide conjugation capability, which hinders the metabolism of Permethrin.

**Etofenprox: CAS# 80844-07-1 (Pyrethroid)**
Etofenprox is a non-ester pyrethroid insecticide with comparable toxicity and a similar mode of action to other pyrethroids.

**Amitraz: CAS#33089-61-1 (Formamide)**
Amitraz is a formamide insecticide that acts by inhibiting mono amine oxidase enzyme and as an octopamine agonist.

**Insect Growth Regulators**
Insect Growth Regulators are considered a biochemical pesticide because rather than controlling target pests through direct toxicity, they interfere with an insect’s life cycle and prevent it from reaching maturity or reproducing.

**Pyriproxyfen: CAS#95737-68-1 (IGR)**
Pyriproxyfen is a juvenile hormone analog (JHA) and a fenoxycarb derivative in which part of the aliphatic chain has been replaced by pyridyl oxyethylene. It functions as an insecticide by overloading the hormonal system of the target insect. The molting hormone and the juvenile hormone (JH) are two major insect-hormones that act to control metamorphosis. High concentrations of JH and low concentrations of molting hormone cause molting larva to continue growing as larval instars. JH prevents the insect from becoming an adult before it is fully grown and abnormal amounts of JH often result in the eventual death of the larva. Pyriproxyfen mimics the action of the juvenile hormones on a number of physiological processes, and is a potent inhibitor of embryogenesis, metamorphosis and adult formation.

**Methoprene: CAS#40596-69-8 (IGR)**
Methoprene is an insect growth regulator that interferes with the normal maturation of insects by preventing them from completing their life cycle and reaching adulthood, thus ultimately preventing them from reproduction. Reported sub-lethal effects from methoprene usage include abnormal morphology and development, reduced fertility, alterations in pheromone production, and altered behavior patterns. S-methoprene halts the growth of chitin, which comprises the
exoskeleton of insects. IGRs are non-toxic to humans since mammals do not produce chitin. These insect growth regulators are found in high concentrations in the hemolymph of particular stages of larval insects, where their function is to maintain the larval stage or prevent metamorphosis. The intensity of the response differs among insects, but generally it is the last instar of larvae or nymph, or pupal stages, which are most affected by methoprene.

**Fipronil: CAS#120068-37-3 (Phenylpyrazole)**
Fipronil is a channel blocker that blocks GABA-gated chloride channels and glutamate-activated chloride channels (GluCls). Fipronil is a broad use insecticide that belongs to the phenylpyrazole chemical family. It works by disrupting the normal function of the central nervous system in insects and is more toxic to insects than people and pets because it is more likely to bind to insect nerve endings. Phenylpyrazoles are inhibitors of a key neurotransmitter in the central nervous system, gamma-aminobutyric acid (GABA). This mechanism also exists in mammals and other vertebrates; however, phenylpyrazoles seem to be much less effective on GABA receptors in vertebrates than in invertebrates. For dogs and cats, the absorption of topically administered fipronil is usually no more than 5% of the administered dose.

**Piperonyl Butoxide: CAS#51-03-6 (Synergist)**
Piperonyl butoxide (PBO) is a synergist used to increase the potency of insecticides like pyrethrins and pyrethroids. PBO acts as a synergist by inhibiting the activity of a family of enzymes called P450s. These enzymes have many functions, including breakdown of toxic chemicals and transformation of hormones. Piperonyl butoxide acts as a synergist by slowing the breakdown in insects of certain insecticides. The oxidation by a family of enzymes called the P450 monooxygenases is the first step in the breakdown of many drugs, pesticides, and other compounds. PBO inhibits the activity of these enzymes. If the breakdown product is less toxic than the insecticide itself, the insecticide remains toxic longer when PBO inhibits the P450 enzymes. P450 enzymes have important biological functions including detoxification of synthetic compounds, and transforming sex hormones, vitamins, and other naturally occurring molecules.

**Imidacloprid: CAS# 138261-41-3 (Neonicotinoid)**
Imidacloprid is a neonicotinoid insecticide in the chloronicotinyl nitroguanidine chemical family. Neonicotinoids are synthetic forms of nicotine, and act on the nicotinic receptors of the nervous system by causing nerves to fire continually until they fail. The chemical takes the place of the normal neurotransmitter acetylcholine in the receptors, which cannot be deactivated by acetylcholinesterase and remains irreversibly blocked. This leads to an over stimulation of the nerve cells, to paralysis and to death of the affected insect. These receptors are found in the central and peripheral nervous system of mammals, but only in the central nervous systems of insects. Neonicotinoids are relatively safe for animals and humans because they bind much more strongly to insect receptors than to mammal receptors.

**Dinotefuran: CAS#165252-70-0 (Neonicotinoid)**
Dinotefuran is an agonist of the nicotinic acetylcholine receptors. It takes the place of the normal neurotransmitter acetylcholine in the receptors, which cannot be deactivated by acetylcholinesterase and remains irreversibly blocked. This leads to an over stimulation of the nerve cells, to paralysis and to death of the affected insect. Dinotefuran does not inhibit
cholinesterase or interfere with sodium channels; therefore, its mode of action is different from those of organophosphate, carbamate, and pyrethroid compounds. It is suggested that Dinotefuran affects the nicotinic acetylcholine binding in a mode that differs from other neonicotinoid insecticides.

**Metaflumizone: CAS#139968-49-3 (Semicarbazone)**
Metaflumizone is in the semicarbazone class of chemicals and acts by blocking the sodium channel of the nervous system causing paralysis of the insect.

**Alternatives to Flea and Tick products**
Consider other non-pesticide treatments when the risks (adverse reactions – agitation, skin irritation, vomiting, diarrhea, death) of the pesticide outweigh the benefits (flea and tick preventative). There are several ways to reduce or eliminate fleas inside the house. Vacuuming carpets, cushioned furniture, and cracks and crevices on floors on a daily basis will help to remove eggs, larvae and adults. Steam cleaning carpets can also kill fleas at any stage in the life cycle. Pet bedding and other places where pets lie should be washed in hot, soapy water every two to three weeks. In the event of a severe infestation, old pet bedding should be discarded and replaced with fresh, clean material. Flea combs are effective in that they allow hair to pass through the tines but not the fleas, thus removing fleas, flea feces and dried blood. Fleas that are removed from pets should be deposited in hot soapy water to kill them.

The Centers for Disease Control and Prevention suggests several ways to reduce ticks in the yard. Tick Safe Zones can be created by modifying the landscape. Play areas should be kept away from shrubs, bushes and other vegetation. Leaf litter should be removed regularly and wood chips or gravel can be placed between lawns and wooded areas to keep ticks away from recreational areas. Play areas and playground equipment should be kept away from shrubs, bushes, and other vegetation. Removing plants that attract deer and constructing physical barriers may help discourage deer from enter the yard and carrying ticks with them.

**Community Service action: Identifying and reporting which flea and tick products should be avoided and removed from the market**

The following data of the 2008 Reported Incidents for Flea and Tick products for Cats and Dogs has been collected from the United States Environmental Protection Agency on April 1, 2010. Although a total of approximately 43,000 incidents were reported for 2008, there were only 23,568 Reported Incidents recorded by the EPA as demonstrated by this chart. We propose a means of obtaining more accurate and thorough reports of adverse effects of flea and tick spot-on treatments. Within each package of Flea and Tick spot-on treatments, there should be a form for the consumers to fill out and submit to the EPA in the event of an adverse reaction. The form will be sent directly to the EPA rather than the companies to avoid a conflict of interest. An unbiased party, such as the EPA, is necessary to ensure that each and every adverse event is accounted for and documented thoroughly according to the product name, company, EPA Registration Number, breed of the animal, and size of the animal. This system will be applicable to all pet care companies that sell Flea and Tick spot-on treatments. We believe that it is essential to obtain accurate information of the negative impacts spot-on treatments pose on companion animals in order to identify potentially harmful products, pesticides, or dosage of pesticides. This
information will enable the EPA to target the products that should be declared inactive and recalled from the market. An efficient means of identifying products that should be inactive will help to reduce the total number of adverse effects experienced by companion animals and save lives.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>EPA Reg. No.</th>
<th>Active Ingredients</th>
<th>Dosage</th>
<th>Total number of Complaints (as of 2008)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sergeant’s Cyphenothrin + IGR Squeeze-on for Dogs</td>
<td>2517-80</td>
<td>Cyphenothrin: 40.00%</td>
<td>1.5 mL, 3.0 mL, 4.5 mL, 6.0 mL</td>
<td>9487 Inactive (FEBRUARY 06, 2013)</td>
<td></td>
</tr>
<tr>
<td>Sergeant’s Cyphenothrin Squeeze-on for Dogs</td>
<td>2517-85</td>
<td>Cyphenothrin: 40.00%</td>
<td>1.5 mL, 3.0 mL, 4.5 mL, 6.0 mL</td>
<td>1175 Inactive (FEBRUARY 06, 2013)</td>
<td></td>
</tr>
<tr>
<td>Marketquest One Drop Flea &amp; Tick Control with Nylar IGR</td>
<td>2517-87</td>
<td>Permethrin: 45.00% Pyriproxyfen: 1.90%</td>
<td>1.0 mL, 1.5 mL, 3.0 mL, 4.5 mL</td>
<td>NP Active (MARCH 17, 2003)</td>
<td></td>
</tr>
<tr>
<td>Sergeant’s Perfect Squeeze-on Flea Control for Cats and Kittens</td>
<td>2517-88</td>
<td>Pyriproxyfen: 2.20%</td>
<td>1.4 mL</td>
<td>NP Active (JANUARY 31, 2005)</td>
<td></td>
</tr>
<tr>
<td>Sergeant’s Squeeze-on Flea &amp; Tick Control for Dogs and Puppies</td>
<td>2517-89</td>
<td>Permethrin: 45.00% Pyriproxyfen: 1.90%</td>
<td>1.0 mL, 1.5 mL, 3.0 mL, 4.5 mL</td>
<td>NP Active (JANUARY 03, 2006)</td>
<td></td>
</tr>
<tr>
<td>Sergeant’s Bansect Squeeze-on for Dogs and Puppies</td>
<td>2517-93</td>
<td>Permethrin: 45.00%</td>
<td>1.5 mL, 3.0 mL, 6.0 mL</td>
<td>NP Active (MARCH 09, 2007)</td>
<td></td>
</tr>
<tr>
<td>Sergeant's Gold Squeeze-On for Dogs</td>
<td>2517-94</td>
<td>Permethrin: 45.00% Pyriproxyfen: 1.90%</td>
<td>1.5 mL, 3.0 mL, 4.5 mL, 6.0 mL</td>
<td>40 Active (MARCH 09, 2007)</td>
<td></td>
</tr>
<tr>
<td>Sergeant’s Cyphenothrin + Methoprene Squeeze-on for</td>
<td>2517-127</td>
<td>Cyphenothrin: 20.00% (S)-Methoprene: 2.30%</td>
<td>1.5 mL, 3.0 mL, 4.5 mL</td>
<td>NP Active (APRIL 30, 2010)</td>
<td></td>
</tr>
<tr>
<td>Dogs (20%)</td>
<td>2517-128</td>
<td>Cyphenothrin: 30.00%</td>
<td>NP</td>
<td>Active (APRIL 30, 2010)</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Sergeant’s Cyphenothrin + Methoprene Squeeze-on for Dogs (30%)</td>
<td>2517-129</td>
<td>Cyphenothrin: 20.00%</td>
<td>1.5 mL, 3.0 mL, 4.5 mL</td>
<td>NP</td>
<td>Active (APRIL 30, 2010)</td>
</tr>
<tr>
<td>Sergeant’s Cyphenothrin + Pyriproxyfen Squeeze-on for Dogs (20%)</td>
<td>2517-130</td>
<td>O,O-Diethyl O-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate: 15.00%</td>
<td>23.10 g</td>
<td>NP</td>
<td>Inactive (NOVEMBER 15, 2001)</td>
</tr>
<tr>
<td>Sergeant’s Double Duty Reflecting Flea &amp; Tick Collar</td>
<td>2517-131</td>
<td>Cyphenothrin: 20.00%</td>
<td>1.5 mL, 3.0 mL, 4.5 mL</td>
<td>NP</td>
<td>Active (APRIL 30, 2010)</td>
</tr>
<tr>
<td>Sergeant’s Cyphenothrin Squeeze-on For Dogs (20%)</td>
<td>2517-132</td>
<td>Cyphenothrin: 30.00%</td>
<td>1.5 mL, 3.0 mL, 6.0 mL</td>
<td>NP</td>
<td>Active (APRIL 30, 2010)</td>
</tr>
<tr>
<td>Sergeant’s Etofenprox/Nylar spot-on Flea &amp; Tick for Dogs &amp; Puppies</td>
<td>2517-133</td>
<td>Etofenprox: 55.00%</td>
<td>2.0 mL, 4.0 mL</td>
<td>NP</td>
<td>Active (APRIL 30, 2010)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil+ Methoprene Squeeze-on for Dogs</td>
<td>2517-134</td>
<td>Fipronil: 9.80%</td>
<td>0.67 mL, 1.34 mL, 2.68 mL, 4.02 mL</td>
<td>NP</td>
<td>Active (NOVEMBER 04, 2010)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + (S)-Methoprene Spot-on for Cats</td>
<td>2517-135</td>
<td>Fipronil: 9.80%</td>
<td>0.50 mL</td>
<td>NP</td>
<td>Active (JANUARY 28, 2011)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil Squeeze-on for Dogs</td>
<td>2517-136</td>
<td>Fipronil: 9.70%</td>
<td>0.67 mL, 1.34 mL, 2.68 mL, 4.02 mL</td>
<td>NP</td>
<td>Active (NOVEMBER 04, 2010)</td>
</tr>
<tr>
<td>Sergeant’s</td>
<td>2517-137</td>
<td>Fipronil: 9.70%</td>
<td>0.50 mL</td>
<td>NP</td>
<td>Active</td>
</tr>
<tr>
<td>Description</td>
<td>Code</td>
<td>Active Ingredient(s) and Concentration</td>
<td>Volume Options</td>
<td>NP Status</td>
<td>Active Date</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
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<td>-------------------------</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Cyphenothrin Squeeze-on for Dogs</td>
<td>2517-140</td>
<td>Fipronil: 9.80% Cyphenothrin: 5.20%</td>
<td>0.67 mL, 1.34 mL, 2.68 mL, 4.02 mL</td>
<td>NP</td>
<td>(JANUARY 13, 2011)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Nylar Squeeze-on for Dogs</td>
<td>2517-141</td>
<td>Fipronil: 9.80% Pyriproxyfen: 2.00%</td>
<td>0.67 mL, 1.34 mL, 2.68 mL, 4.02 mL</td>
<td>NP</td>
<td>(MARCH 23, 2011)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Cyphenothrin + Methoprene Squeeze-on for Dogs</td>
<td>2517-142</td>
<td>Fipronil: 9.80% Cyphenothrin: 5.20% (S)-Methoprene: 76.2%</td>
<td>0.67 mL, 1.34 mL, 2.68 mL, 4.02 mL</td>
<td>NP</td>
<td>(MARCH 23, 2011)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Cyphenothrin + Nylar Squeeze-on for Dogs</td>
<td>2517-143</td>
<td>Fipronil: 9.80% Cyphenothrin: 5.20% Pyriproxyfen: 2.00%</td>
<td>0.67 mL, 1.34 mL, 2.68 mL, 4.02 mL</td>
<td>NP</td>
<td>(MARCH 22, 2011)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Etofenprox + Methoprene Spot-on for Cats</td>
<td>2517-145</td>
<td>Fipronil: 9.80% Etofenprox: 15.00% (S)-Methoprene: 11.80%</td>
<td>0.50 mL</td>
<td>NP</td>
<td>(AUGUST 18, 2011)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Pyriproxyfen Spot-on for Cats</td>
<td>2517-146</td>
<td>Fipronil: 9.80% Pyriproxyfen: 2.20%</td>
<td>0.50 mL</td>
<td>NP</td>
<td>(AUGUST 18, 2011)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Etofenprox + Pyriproxyfen Spot-on for Cats</td>
<td>2517-147</td>
<td>Fipronil: 9.80% Etofenprox: 15.00% Pyriproxyfen: 2.20%</td>
<td>0.50 mL</td>
<td>NP</td>
<td>(AUGUST 18, 2011)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Etofenprox Spot-on for Cats</td>
<td>2517-148</td>
<td>Fipronil: 9.80% Etofenprox: 15.00%</td>
<td>0.50 mL</td>
<td>NP</td>
<td>(AUGUST 18, 2011)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Cyphenothrin (8.2%) + Methoprene Squeeze-on for</td>
<td>2517-149</td>
<td>Fipronil: 9.80% Cyphenothrin: 8.20% (S)-Methoprene: 8.80%</td>
<td>0.67 mL, 1.34 mL, 2.68 mL, 4.02 mL</td>
<td>NP</td>
<td>(APRIL 25, 2012)</td>
</tr>
<tr>
<td>Description</td>
<td>Code</td>
<td>Active Ingredient</td>
<td>Volume</td>
<td>NP</td>
<td>Active Date</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>----------</td>
<td>----------------------------------</td>
<td>-----------------</td>
<td>----</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Cyphenothrin (8.2%) + Pyriproxyfen Squeeze-on for Dogs</td>
<td>2517-150</td>
<td>Fipronil: 9.80% Cyphenothrin: 8.20% Pyriproxyfen: 2.00%</td>
<td>0.67 mL, 1.34 mL, 2.68 mL, 4.02 mL</td>
<td>NP</td>
<td>Active (APRIL 25, 2012)</td>
</tr>
<tr>
<td>Sergeant’s Fipronil + Cyphenothrin (8.2%) Squeeze-on for Dogs</td>
<td>2517-151</td>
<td>Fipronil: 9.80% Cyphenothrin: 8.20%</td>
<td>0.67 mL, 1.34 mL, 2.68 mL, 4.02 mL</td>
<td>NP</td>
<td>Active (APRIL 25, 2012)</td>
</tr>
<tr>
<td>Hartz Advanced Care OneSpot Flea Egg and Larvae Treatment for Cats &amp; Kittens</td>
<td>2596-147</td>
<td>(S)-Methoprene: 2.90%</td>
<td>1.0 mL</td>
<td>274</td>
<td>Active (MAY 14, 1998)</td>
</tr>
<tr>
<td>Hartz Advanced Care Brand Flea &amp; Tick Drops for Dogs &amp; Puppies</td>
<td>2596-150</td>
<td>Phenothrin: 85.70% (S)-Methoprene: 2.30%</td>
<td>1.0 mL, 1.3 mL, 4.1 mL, 5.9 mL</td>
<td>322</td>
<td>Active (JANUARY 23, 2000)</td>
</tr>
<tr>
<td>Hartz Flea &amp; Tick Drops for Dogs &amp; Puppies</td>
<td>2596-151</td>
<td>Phenothrin: 85.70%</td>
<td>1.0 mL, 1.3 mL</td>
<td>501</td>
<td>Active (NOVEMBER 22, 2000)</td>
</tr>
<tr>
<td>Hartz UltraGuard Plus + Flea &amp; Tick Drops for Dogs &amp; Puppies</td>
<td>2596-156</td>
<td>Phenothrin: 85.70% Pyriproxyfen: 0.5%</td>
<td>1.0 mL, 1.9 mL, 4.1 mL, 6.3 mL</td>
<td>NP</td>
<td>Active (MAY 28, 2008)</td>
</tr>
<tr>
<td>Hartz UltraGuard Pro Flea &amp; Tick Treatment for Dogs &amp; Puppies</td>
<td>2596-159</td>
<td>Phenothrin: 85.70% (S)-Methoprene: 2.30% Pyriproxyfen: 0.5%</td>
<td>1.0 mL, 1.9 mL, 4.1 mL, 6.3 mL</td>
<td>NP</td>
<td>Active (SEPTEMBER 16, 2008)</td>
</tr>
<tr>
<td>Hartz UltraGuard Flea &amp; Tick Topical Treatment for Dogs</td>
<td>2596-163</td>
<td>Fipronil: 9.70%</td>
<td>0.67 mL, 1.34 mL, 2.68 mL, 4.02 mL</td>
<td>NP</td>
<td>Active (JULY 09, 2012)</td>
</tr>
<tr>
<td>Hartz Fieldforce Topical Solution for Cats &amp; Kittens</td>
<td>2596-164</td>
<td>Fipronil: 9.70%</td>
<td>1.0 mL</td>
<td>NP</td>
<td>Active (JULY 09, 2012)</td>
</tr>
<tr>
<td>Hartz Fieldforce</td>
<td>2596-165</td>
<td>Fipronil: 9.80%</td>
<td>0.67 mL</td>
<td>NP</td>
<td>Active (JULY 09, 2012)</td>
</tr>
<tr>
<td>Product Name</td>
<td>Active Ingredients</td>
<td>Quantity</td>
<td>Exp. Date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-------------------------------------------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual action Topical Solution for Dogs</td>
<td>(S)-Methoprene: 8.80%</td>
<td>1.34 mL, 2.68 mL, 4.02 mL</td>
<td>09, 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartz Fieldforce Dual action Topical Solution for Cats &amp; Kittens</td>
<td>Fipronil: 9.80% (S)-Methoprene: 11.80%</td>
<td>1.0 mL</td>
<td>NP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartz First Defense Topical Solution for Dogs &amp; Puppies</td>
<td>Etofenprox: 55.00% Piperonyl Butoxide: 10.00% N-octyl bicycloheptene dicarboximide: 1.00% Pyriproxyfen: 0.5%</td>
<td>0.91 mL, 1.95 mL, 3.9 mL, 6.5 mL</td>
<td>NP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartz UltraGuard Plus Dual Active Flea &amp; Tick Drops for Dogs &amp; Puppies</td>
<td>Etofenprox: 55.00% Piperonyl Butoxide: 10.00% N-octyl bicycloheptene dicarboximide: 1.00% Pyriproxyfen: 0.5% (S)-Methoprene: 0.25%</td>
<td>0.91 mL, 1.95 mL, 3.9 mL, 6.5 mL</td>
<td>NP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartz UltraGuard PRO Triple Active Flea &amp; Tick Drops for Dogs &amp; Puppies</td>
<td>Etofenprox: 55.00% Piperonyl Butoxide: 10.00% N-octyl bicycloheptene dicarboximide: 1.00% Pyriproxyfen: 0.5% (S)-Methoprene: 0.25%</td>
<td>0.91 mL, 1.95 mL, 3.9 mL, 6.5 mL</td>
<td>NP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartz Dual Action Topical Drops for Cats &amp; Kittens</td>
<td>Etofenprox: 40.00% (S)-Methoprene: 3.6%</td>
<td>1.0 mL</td>
<td>NP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zodiac Spot-on Flea Control for Cats &amp; Kittens</td>
<td>(S)-Methoprene: 3.6%</td>
<td>1.0 mL</td>
<td>128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zodiac Spot On Plus Flea &amp; Tick Control for Cats</td>
<td>Permethrin: 45.00% (S)-Methoprene: 3.00%</td>
<td>1.0 mL, 2.0 mL, 3.0 mL</td>
<td>463</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Name</td>
<td>Stock Number</td>
<td>Active Ingredients</td>
<td>Dosage</td>
<td>Stock</td>
<td>Status</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------</td>
<td>--------------------</td>
<td>------------</td>
<td>------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Zodiac Multi-Cat Spot On Plus Flea &amp; Tick Control for Cats</td>
<td>2724-504</td>
<td>(S)-Methoprene: 3.60% Etofenprox: 40.00%</td>
<td>1.0 mL, 1.8 mL</td>
<td>621</td>
<td>Active (JANUARY 18, 2006)</td>
</tr>
<tr>
<td>Advantage 9 Topical Solution for Small Cats</td>
<td>11556-116</td>
<td>Imidacloprid: 9.10%</td>
<td>0.4 mL</td>
<td>670</td>
<td>Active (MARCH 08, 1996)</td>
</tr>
<tr>
<td>Advantage 10 Topical Solution for Small Dogs</td>
<td>11556-117</td>
<td>Imidacloprid: 9.10%</td>
<td>0.4 mL</td>
<td>304</td>
<td>Active (MARCH 08, 1996)</td>
</tr>
<tr>
<td>Advantage II for Dogs</td>
<td>11556-128</td>
<td>Imidacloprid: 9.10% Pyriproxyfen: 0.46%</td>
<td>0.4 mL</td>
<td>NP</td>
<td>Active (SEPTEMBER 18, 2007)</td>
</tr>
<tr>
<td>K9 Advantix 10</td>
<td>11556-132</td>
<td>Imidacloprid: 8.80 % Permethrin: 44.0%</td>
<td>0.4 mL</td>
<td>1645</td>
<td>Active (SEPTEMBER 30, 2002)</td>
</tr>
<tr>
<td>Frontline Top Spot for Cats</td>
<td>65331-2</td>
<td>Fipronil: 9.70%</td>
<td>0.5 mL</td>
<td>152</td>
<td>Active (MAY 31, 1996)</td>
</tr>
<tr>
<td>Frontline Top Spot for Dogs</td>
<td>655331-3</td>
<td>Fipronil: 9.70%</td>
<td>0.67 mL, 1.34 mL, 4.02 mL</td>
<td>255</td>
<td>Active (JUNE 04, 1996)</td>
</tr>
<tr>
<td>Frontline Plus for Cats</td>
<td>655331-4</td>
<td>Fipronil: 9.80% (S)-Methoprene: 11.80%</td>
<td>0.50 mL</td>
<td>1305</td>
<td>Active (JULY 21, 2000)</td>
</tr>
<tr>
<td>Frontline Plus for Dogs</td>
<td>655331-5</td>
<td>Fipronil: 9.80% (S)-Methoprene: 8.80%</td>
<td>0.023 fl. Oz, 0.045 fl. Oz, 0.091 fl. Oz, 0.136 fl. Oz</td>
<td>2469</td>
<td>Active (JULY 21, 2000)</td>
</tr>
<tr>
<td>Vectra 3D for Dogs &amp; Puppies</td>
<td>83399-6</td>
<td>Dinotefuran: 4.95% Pyriproxyfen: 0.44% Permethrin: 36.08%</td>
<td>1.6 mL, 3.6 mL, 4.7 mL, 8.0 mL</td>
<td>721</td>
<td>Active (JULY 13, 2007)</td>
</tr>
<tr>
<td>Promeris Spot-on for Dogs</td>
<td>80490-2</td>
<td>Metaflumizone: 14.34% Amitraz: 14.34%</td>
<td>0.023 fl. Oz, 0.045 fl. oz, 0.113 fl. Oz, 0.180 fl. Oz, 0.225 fl. Oz</td>
<td>2820</td>
<td>Inactive (SEPTEMBER 28, 2011)</td>
</tr>
</tbody>
</table>
Dr. Thomas H. Zachos,
U. S. EPA, Region 2
Pesticides and Toxic Substances Branch
2890 Woodbridge Avenue, MS-500
Edison, NJ 08837

From your position title at the EPA, we assume that it is one of your responsibilities to help ensure the safety and welfare of the citizens by regulating pesticides and the products that contain these chemicals. Rising concerns of the toxicity of Flea and Tick products for companion animals was triggered by an influx of incident reports of adverse effects from thesepreventatives. Due to an increase in the number of reports of adverse reactions to certain products, the Environmental Protection Agency distributed an advisory concerning ~70 spot-on flea and tick control products in April of 2009. It is not clear, however, that the consumers purchasing these products have been advised. Most consumers just assume if they can purchase the product, that they are safe for the usage that they were intended (as they are regulated by the EPA).

Although some Flea and Tick products have been deemed inactive by the EPA, some of them are still currently available in stores. As of February 2013, Sergeant’s Gold Squeeze on for Dogs, which contains 40% cyphenothrin and 2% pyriproxyfen, is now listed as being “inactive.” Both Promeris Spot On for Cats and Dogs were inactivated by the EPA on September 28, 2011. Although these products are no longer being manufactured, we have experienced an adverse effect first-hand from Sergeant’s product EPA Reg. No. 2517-80.

The pet owner had purchased from Acme Markets in PA Sergeant’s Gold flea and tick squeeze-on for dogs with the EPA Reg. No 2517-80. The product purchased was for dogs between 40-60 lbs. In May 2013, the pet owner, wearing latex gloves, applied the product as described on the packaging to her 48 lb. long-haired purebred dog. That day and several days following, the dog paced incessantly - like she didn’t know what to do with herself.
It was when the vomiting started, as did an uncontrollable diarrhea on the home’s white carpeting that prompted the pet owner to look on the back of the packaging and call the number that was supplied. A person named Wayne answered and the pet owner described what the dog was experiencing. He said that it was likely an “allergic reaction” and that “the area” should be washed with Dawn or Palmolive. He said that the “drug” “just” stays on the skin and hair and protects the dog from fleas and ticks by the product being in the natural oils of the skin. The pet owner replied that the product must be inside the dog’s body to cause vomiting and diarrhea. Wayne said that that was likely just an allergic reaction and that it didn’t “go systemic”. He then said “thank you, and was there anything else he could help with”, the premise to hanging up.

Outraged, the pet owner asked why he hadn’t asked what exactly the product was that had sickened the dog, or taken my name. Clearly, without that information, he would not be able to file an incident report. The pet owner then requested that he take the pet owner’s name and the product number and that he file some sort of product complaint.

Since there are no requirements that the spot-on products containing pesticides actually be tested on dogs or cats, there is no guarantee that these products will not harm companion animals. Many consumers are uninformed of the hazardous effects of these products, and it is the responsibility of the EPA as well as the pet care companies that are manufacturing these products to increase awareness and conduct better pre-market clinical trials and post market surveillance.

We are writing a paper on the matter and are just about to upload a YouTube video to warn consumers of the potential risks associated with the spot-on flea and tick control products.

In our paper, we suggest that the manufacturers of these potentially toxic products engage the consumers using these products to become “citizen scientists” and report to the manufacturer (and the EPA), their experience with the product – good and bad. The manufacturers could offer some incentive in the packaging (like to receive a coupon for a free product from any manufacturer) if they provided their input.

We are interested in hearing from you about our citizen science idea to maybe bring such a program to fruition.

Sincerely,

Nicole Dziedzic and Dr. Julie Fagan Ph. D. 

fagan@rutgers.edu
Avivah:

Good speaking with you this afternoon. I am working on a paper with my student Nicole (cc'd) on the topic of Spot-On Flea and Tick products. We had some questions and would appreciate your forwarding our questions to the appropriate people at EPA.

1. There were 43,000 reported incidents for these products in 2008, yet less than 20,000 were accounted for in EPA's reported list. Regarding the other 25,000+ incidents - were they ascribed to a particular product - how do you account for them?

2. The number of complaints for flea and tick spot on products was reported on an EPA website in 2008. It is now 2013 - is there an updated list - like in the year 2012?

3. Surely in 5 years there are newer spot-on flea and tick control products on the market. What might these be and do you have incident reports on these? Are there "drugs" under the auspices of the FDA that contain the pesticides in spot-on flea and tick control products that we should know about - and are incident reports available for those as well?

4. Going from an “active” to an “inactive” product:
   a. Who makes this determination?
   b. How does this come about - have anything to do with the number of reported complaints?
   c. Is there a magic number to move the product from active to inactive?
   d. How does the EPA define "inactive"
   e. Once Inactive, what is required of the company which sells the product containing the inactive pesticide? Do they just not manufacture more? Are they allowed to sell (ship out to stores) what they've already manufactured? Are they advised to remove the product from stores that are selling the product?

5. Regarding the number of incidents per product, you really need to know the denominator of the equation - how many products were sold. If there were 40 reported incidents and they only sold 40, that would need 100% had problems with it vs 40 incidents for every 40,000 sold.

6. When an animal experiences an adverse reaction, such as vomiting and diarrhea, it is evident that the product that was applied topically has been internalized. Washing the pet would not necessarily eliminate whatever toxic effects it may have had to organs, etc. Comment? We
understand that these products do not have to be tested on the intended target (dog, cat) which, is alarming. Comment?

See our video on the subject: http://www.youtube.com/watch?v=BsyY3o8-d9c

We also have some suggestions on how to better report incidents. Who might we send our recommendations to?

Thank you,

Julie M. Fagan, Ph.D.
Department of Animal Sciences
Rutgers, The State University of New Jersey
84 Lipman Dr.
New Brunswick, NJ 08903

Below is their response (indicated in bold) to our request for information sent on July 30, 2013 that was received 3.5 months later.

---------------------------- Original Message ----------------------------
Subject: Response to your July 30 email to Avivah Jakob with questions regarding spot-on products
From: "Overbey, Dian" <Overbey.Dian@epa.gov>
Date: Wed, November 13, 2013 5:16 pm
To: "fagan@rutgers.edu" <fagan@rutgers.edu>
Cc: "Keller, Kaitlin" <Keller.Kaitlin@epa.gov>
"Overstreet, Anne" <overstreet.anne@epa.gov>
"Dinkins, Darlene" <Dinkins.Darlene@epa.gov>

Dr. Fagan:

Attached (below) is our response (in bold) to your email to Ms. Jakob. We apologize for the long delay (3.5 months) but hope this information is helpful to you. If you have further questions, please feel free to contact me.

Dian D. Overbey

From: fagan@rutgers.edu [mailto:fagan@rutgers.edu]
Sent: Tuesday, July 30, 2013 3:21 PM
To: Jakob, Avivah
Cc: Nicole Dziedzic
Subject: Questions regarding spot on products

Avivah:
Good speaking with you this afternoon. I am working on a paper with my student Nicole (cc'd) on the topic of Spot-On Flea and Tick products. We had some questions and would appreciate your forwarding our questions to the appropriate people at EPA.

1. There were 43,000 reported incidents for these products in 2008, yet less than 20,000 were accounted for in EPAs reported list. Regarding the other 25,000+ incidents - were they ascribed to a particular product - how do you account for them?

RESPONSE: In preparation for conducting an in-depth evaluation of spot-on products for which incidents had been reported EPA compiled a list and asked the registrants for enhanced reporting on incidents involving those products. However, not all of the data requested by the EPA were available for all of the products. Some information was not commonly collected by the registrants or the pet owner did not have the information available.

The following are examples of incidents that were generally not included:
- Incidents with no EPA registration number
- Incidents from other countries
- Efficacy reports (reports that product didn’t work to kill fleas and ticks)
- Incidents that were considered generally ambiguous
- Incidents that also involved use of other products or drugs because effects may have been associated with the other product
- Incidents that involved multiple animals because it was difficult to tell which animal was affected and to what degree
- Multiple reports or contacts with a registrant for the same incident

2. The number of complaints for flea and tick spot on products was reported on an EPA website in 2008. It is now 2013 - is there an updated list - like in the year 2012?

RESPONSE: Aggregate annual incidents for pet spot-on products are as follows:

<table>
<thead>
<tr>
<th>Year</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Aggregate Incidents</td>
<td>28,897</td>
<td>44,322</td>
<td>37,968</td>
<td>28,118</td>
<td>27,064</td>
</tr>
</tbody>
</table>

These numbers may change periodically due to late incident report submissions or reports that may have been updated with additional information after the initial submission. The compilation of figures for 2012 has not yet been completed.

3. Surely in 5 years there are newer spot-on flea and tick control products on the market. What might these be and do you have incident reports on these?
RESPONSE: There have been new spot-on flea and tick control products registered. Some are the result of fipronil going off patent. Some registrants have reformulated previously registered products, with the new products containing reduced percentages of one or more active ingredients. Some have a new active ingredient. The list of registered spot-on products can be found at [http://www2.epa.gov/pets/list-spot-flea-and-tick-products](http://www2.epa.gov/pets/list-spot-flea-and-tick-products).

Section 6(a)(2) of FIFRA requires that, “If at any time after the registration of a pesticide the registrant has additional factual information regarding the pesticide, the registrant shall submit such information to the Administrator [of the EPA].” If any of the recently registered products are implicated in adverse incidents, the registrant must report the incidents to the EPA. All spot-on registrants are required to submit quarterly sales and enhanced incident reports in addition to the 6(a)(2) submissions. Quarterly enhanced incident reporting for flea and tick product manufacturers includes detailed requirements beyond those of section 6(a)(2), such as the animal’s breed, age, and weight; if it was the first time the product was used; where the product was purchased; any potential misuse; and the outcome. Enhanced reporting additionally requires an analysis of the incidents.

Are there "drugs" under the auspices of the FDA that contain the pesticides in spot-on flea and tick control products that we should know about - and are incident reports available for those as well?

RESPONSE: There are animal drug products approved by the FDA that contain active ingredients found in EPA-registered spot-on flea and tick control pesticide products. The FDA collects data on incidents resulting from the use of those products that they regulate.

4. Going from an “active” to an “inactive” product:

RESPONSE: The EPA does not use the term “inactive” with regard to pesticide registrations. Products that are registered by the EPA and for which the registrant pays the annual maintenance fee are active registrations. The registrant may not actually manufacture or market a product, but as long as the registrant pays the annual maintenance fee, the registration is considered active.

Products for which maintenance fees are not paid are canceled.

a. Who makes this determination?
b. How does this come about - have anything to do with the number of reported complaints?
c. Is there a magic number to move the product from active to inactive?
d. How does the EPA define "inactive"
e. Once Inactive, what is required of the company which sells the product containing the inactive pesticide? Do they just not manufacture more?

Are they allowed to sell (ship out to stores) what they've already manufactured?
Are they advised to remove the product from stores that are selling the product?
RESPONSE: Over time, registered pesticides, or certain uses of a registered pesticide, have been canceled. These cancellations occur for various reasons:

- Voluntary cancellation by the registrant
- Cancellation by the EPA because required fees were not paid
- Cancellation by the EPA because unacceptable risk existed that could not be reduced by other actions such as voluntary cancellation of selected uses or changes in the way the pesticide is used.

When a product is canceled, the registrant and the EPA reach an agreement about existing stocks. Existing stocks may be allowed to be sold for a specific period of time or the EPA may require that existing stocks be withdrawn from stores.

5. Regarding the number of incidents per product, you really need to know the denominator of the equation - how many products were sold. If there were 40 reported incidents and they only sold 40, that would need 100% had problems with it vs 40 incidents for every 40,000 sold.

RESPONSE:

The EPA did consider the number of units sold when we conducted our evaluation, but we are not able share that information publically since it is confidential. The number of units sold is considered Confidential Business Information under the Federal Insecticide Fungicide and Rodenticide Act.

Section 10 of FIFRA specifies how and to what extent information submitted to the agency under FIFRA may be afforded protection as confidential business information (CBI). FIFRA section 10(b) protects from disclosure “trade secrets and commercial or financial information obtained from a person and privileged or confidential.”

As previously stated, spot-on registrants submit quarterly sales data along with their enhanced incident data to allow for indepth analysis as needed. If we see a high number of incidents, we have the sales data available to help determine its significance.

6. When an animal experiences an adverse reaction, such as vomiting and diarrhea, it is evident that the product that was applied topically has been internalized. Washing the pet would not necessarily eliminate whatever toxic effects it may have had to organs, etc. Comment?

RESPONSE: Research has shown that not all incidences of vomiting and diarrhea are the result of the product applied; some are attributable to the very act of application and the stress on the animal caused by restraining and handling.

Washing a pet that experiences adverse effects is prudent and may help prevent further absorption.

We understand that these products do not have to be tested on the intended target (dog,cat) which, is alarming. Comment?
RESPONSE: The EPA requires that products, including pet spot-on products, be tested on dogs or cats, depending on the intended product use, using EPA’s companion animal safety study, Guideline 870.7200. This study requirement was developed in 1996 to harmonize with requirements for pre-market testing by the FDA Center for Veterinary Medicine. Issues about the companion animal study were presented at a FIFRA Scientific Advisory Panel meeting in October 1996 before the guideline was implemented. The FDA also requires clinical trials in a diverse population of pets, but clinical trials are not presently required by EPA.

The EPA guideline calls for testing at 1X, 3X, and 5X doses of the end use product in six animals per sex of each dose group, with the age of the animals dependent upon label claims. For evaluation of safety, the guideline states: "The targeted adequate margin of safety is 5X. Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g., transient, non-life-threatening signs)."

The EPA guideline states that the companion animal study is intended to demonstrate an adequate margin of safety if the product is misused or overused, to serve as a basis for product labeling, and to assure consistency and fairness in data requirements. Although not explicitly stated in the guideline, the 5X margin of safety is also intended to be protective of effects seen in a larger population because the testing is only done in a small group of animals, which may not always detect toxicity occurring in a larger, more heterogeneous group of animals.

Companion animal studies for the individual spot-on products were re-evaluated during the EPA’s internal and external reviews and it was concluded that this study in its present form has not completely served to predict toxicity seen in incident reports. For example, beagles are frequently used in safety studies (the 870.7200 guidelines do not specify the use of any one breed) but were not among the more sensitive breeds for incidents. Therefore, revisions and additions to the EPA guideline are being considered.

See our video on the subject: [http://www.youtube.com/watch?v=BsyY3o8-d9c](http://www.youtube.com/watch?v=BsyY3o8-d9c)

RESPONSE: In your video, you imply that only conditionally registered pesticide products are subject to registration review. This is not the case. The registration review program makes sure that, as the ability to assess risk evolves and as policies and practices change, ALL registered pesticides are re-evaluated every 15 years to ensure that they meet the statutory standard of no unreasonable adverse effects, and products in the marketplace can still be used safely.

During registration review, EPA considers new studies and information including incident data in updating the human health and ecological risk assessments for a pesticide, as needed. The agency invites public comment and input at several stages of the process; that is, in opening the registration review docket, on draft risk assessments, and on proposed decisions.
The video also states that, “Many reports of major adverse reactions may result in removing (15 years later) pesticides from the ‘Active’ to the ‘inactive’ list”. This is not accurate. The federal pesticide law allows the EPA to act quickly if the data and associated scientific evaluations warrant such action. If the risk posed by a pesticide, supported by the best available, peer-reviewed science, cannot be mitigated or managed through other measures, and the agency determines that the pesticide no longer meets the FIFRA standard for registration, then the agency can move quickly to take appropriate regulatory action.

There should be no inference in your video that the information is sanctioned and/or approved by the EPA. A slide stating who developed the video and that it represents your views would help clarify matters.

We also have some suggestions on how to better report incidents. Who might we send our recommendations to?

RESPONSE: We appreciate your interest in providing suggestions on how to better report incidents. Please send your recommendations to Kaitlin Keller at keller.kaitlin@epa.gov.

EPA also takes reports from members of the public on incidents involving flea and tick pesticide products. For information on how to report incidents, see: http://pesticides.supportportal.com/link/portal/23002/23008/Article/18052/I-applied-a-topical-flea-and-tick-pesticide-to-my-pet-and-it-had-a-bad-reaction-What-should-I-do-How-should-I-report-the-incident.

References

Rising Concerns of the Toxicity of Flea and Tick Spot On Treatments
https://www.avma.org/public/PetCare/Pages/Flea-and-Tick-Products-EPA-FAQs.aspx

Measures implemented by the EPA to promote product safety
https://www.avma.org/public/PetCare/Pages/Flea-and-Tick-Products-EPA-FAQs.aspx

When is it mandatory to recall Flea and Tick Products?
https://www.avma.org/public/PetCare/Pages/Flea-and-Tick-Products-EPA-FAQs.aspx

Who regulates Flea and Tick Treatments?
https://www.avma.org/public/PetCare/Pages/Flea-and-Tick-Products-EPA-FAQs.aspx

How does the EPA Regulate Flea and Tick Treatments?
https://www.avma.org/public/PetCare/Pages/Flea-and-Tick-Products-EPA-FAQs.aspx
http://www.epa.gov/pesticides/food/govt.htm
http://www.epa.gov/pesticides/factsheets/riskassess.htm#step%203

Toxicity tests required by the EPA for pesticide approval
http://www.epa.gov/pesticides/factsheets/riskassess.htm

For more information regarding pesticide approval
http://www.epa.gov/pesticides/factsheets/stprf.htm#information

Drug Approval Process

Flea and Tick Drugs Regulated by the FDA

Who to Contact in the Event of an Adverse Reaction
http://www.epa.gov/pesticides/fifra6a2/
http://www.epa.gov/pesticides/health/petproductseval.html

The detrimental impact of Sergeant’s active ingredient Cyphenothrin
http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html
http://parasitipedia.net/index.php?option=com_content&view=article&id=2462&Itemid=2729

Mechanism of action of cyphenothrin and pyriproxyfen
http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html
http://parasitipedia.net/index.php?option=com_content&view=article&id=2462&Itemid=2729

Other popular flea and tick preventatives
http://www.beyondpesticides.org/infoservices/pesticidefactsheets/toxic/methoprene.php
http://www.cdpr.ca.gov/docs/emon/pubs/methofate.pdf

Mechanism of action of the Active Ingredients in flea and tick preventatives
Cyphenothrin: CAS#39515-40-7 (Pyrethroid)
http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html
http://parasitipedia.net/index.php?option=com_content&view=article&id=2462&Itemid=2729
Phenothrin: CAS# 26002-80-2 (Pyrethroid)
http://npic.orst.edu/factsheets/dphentech.html#mode
http://www.epa.gov/oppsrrd1/REDs/sumithrin_%28d-phenothrin%29_red.pdf

Permethrin: CAS# 52645-53-1 (Pyrethroid)
http://www.inchem.org/documents/pds/pds/pest51_e.htm
http://npic.orst.edu/factsheets/Permtech.pdf
http://www.drugbank.ca/drugs/DB04930

Etofenprox: CAS# 80844-07-1 (Pyrethroid)

Amitraz: CAS# 33089-61-1 (Formamide)

Pyriproxyfen: CAS# 95737-68-1 (IGR)

Methoprene: CAS# 40596-69-8 (IGR)

Fipronil: CAS# 120068-37-3 (Phenylpyrazole)
http://npic.orst.edu/factsheets/fipronil.html#whatis
http://parasitipedia.net/index.php?option=com_content&view=article&id=2465&Itemid=2733

Piperonyl Butoxide: CAS# 51-03-6 (Synergist)

Imidacloprid: CAS# 138261-41-3 (Neonicotinoid)
http://npic.orst.edu/factsheets/imidacloprid.pdf
http://parasitipedia.net/index.php?option=com_content&view=article&id=2467&Itemid=2735

Dinotefuran: CAS# 165252-70-0 (Neonicotinoid)
http://parasitipedia.net/index.php?option=com_content&view=article&id=2470&Itemid=2737
http://www.mitsuichemicals.com/dinotefuran.htm

Metaflumizone: CAS# 139968-49-3 (Semicarbazone)

Alternatives to Flea and Tick products
http://www.epa.gov/pesticides/factsheets/flea-tick.htm
Community Service action: Identifying and reporting which flea and tick products should be avoided and removed from the market

Letter to the Editor
August 1, 2013
USA TODAY
7950 Jones Branch Road
McLean, Va. 22102
703-854-3400

Dear Editor,

Please consider publishing the letter below in USA Today. We believe that this is important information that every pet owner needs to know about. If you have any questions or concerns, please either email or call us. Thank you.

Beware: Flea & Tick Control Products May Harm Your Pet!

Most consumers believe that the flea and tick spot-on control products available for purchase are safe “medicines” and are completely unaware that these products are solely pesticides regulated by the EPA (not the FDA) and DO NOT require testing on dogs or cats prior to being put on the market. Over 43,000 adverse reactions (ranging from skin irritations to agitation, vomiting, diarrhea and death) to flea and tick “spot-on” control products were reported in the year 2008. In 2013, neither the EPA or the manufacturers of these flea and tick preventatives have adequately assured the health and safety of these products by conducting better pre-market clinical trials and post market surveillance nor have they developed a systematic method of reporting adverse reactions to these products. Unless ticks or fleas present as a problem to their pet, perhaps pet owners should consider pesticide-free alternatives. View the Youtube video of the title of this letter "Beware: Flea & Tick Control Products May Harm Your Pet!"

Sincerely,

Nicole Dziedzic and Dr. Julie Fagan Ph. D. Rutgers University 2013
fagan@rutgers.edu